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MECHANISMS OF CARCINOGENESIS

Activation and Metabolism of Carcinogens

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service • National Institutes of Health • National Cancer Institute

HE 20. 3173/2:

METABOLIC ACTIVATION OF CARCINOGENS

1. METABOLIC STUDY OF 7-METHYLBENZO[A]PYRENE WITH RAT LIVER MICROSOMES: SEPARATION BY REVERSED-PHASE AND NORMAL-PHASE HIGH PERFORMANCE LIQUID CHROMATOGRAPHY AND CHARACTERIZATION OF METABOLITES.

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Dept. Pharmacology, Sch. Medicine, Uniformed Services Univ. Health Sciences, Bethesda, MD, 20014

Chem Biol Interact; 36(2):153-166 1981

The 7-methylbenzo[a]pyrene (7-MBaP) was incubated with liver microsomes of rats pretreated with polychlorinated biphenyls (Aroclor 1254) (PCBs). Metabolites of 7-MBaP were isolated by both reversed-phase and normal-phase high performance liquid chromatography (HPLC) and were characterized by nuclear magnetic resonance, UV-visible and mass spectral analyses. The predominant metabolite of 7-MBaP was found to be 3-hydroxy-7-methylbenzo[a]pyrene (3-hydroxy-7-MBaP). Other identified metabolites include 7-MBaP 4,5-, 7,8- and 9,10-trans-dihydrodiols, 7-hydroxymethyl-BaP, 7-hydroxymethyl-BaP trans-9,10-dihydrodiol, 9-hydroxy-7-MBaP 3-hydroxy-7-hydroxymethyl-BaP, 7-MBaP 1,6-and 3,6-quinones and a hydroxyquinone which is also formed by further metabolism of the 3-hydroxy-7-MBaP. Comparative metabolic studies of 7-MBaP and BaP indicated that, relative to that of BaP, the methyl substituent of 7-MBaP slightly increases the formation of 3-hydroxy-7-MBaP and decreases the metabolism at other regions of the 7-MBaP molecule. The finding that a 7,8-dihydrodiol is a metabolite indicates that, like BaP, 7-MBaP may also be activated to the potentially reactive 7,8-dihydrodiol 9,10-epoxides although their formations are significantly reduced. (Author abstract) (22 Refs)

2. METABOLIC FATE AND CARCINOGENICITY OF N-(OMEGA-HYDROXYALKYL)-N-(4 HYDROXYBUTYL)NITROSAMINES, ANALOGS OF N-BUTYL-N-(4-HYDROXYBUTYL)NITROSAMINE, IN THE RAT.

Suzuki E, Takeda Y, Mochizuki M, Hashimoto Y, Okada M
Tokyo Biochemical Res. Inst., Takada 3-41-8, Toshima-ku, Tokyo 171, Japan

Gan; 72(4):539-546 1981

The metabolic fate and carcinogenicity of three omega-hydroxy derivatives of N-alkyl-N-(4-hydroxybutyl)nitrosamines, potent bladder carcinogens, were investigated in the rat. They were N-(2-hydroxyethyl)-N-(4-hydroxybutyl)nitrosamine (HEHBN), N-(3-hydroxypropyl)-N-(4-hydroxybutyl)nitrosamine (HPHBN), and N,N-bis(4-hydroxybutyl)nitrosamine (BHBN). The principal urinary metabolite of HEHBN as well as HPHBN was identified as the corresponding 3-carboxypropyl compound, while the main metabolite of BHBN was N,N-bis(3-carboxypropyl)nitrosamine, indicating the preferential metabolic oxidation of the 4-hydroxybutyl chain to the 3-carboxypropyl group in the N-(omega-hydroxyalkyl)-N-(4-hydroxybutyl)nitrosamines. All three N-nitrosamines having the 4-hydroxybutyl chain induced neither bladder tumor nor any tumor in other organs under conditions similar to those used for N-alkyl-N-(4-hydroxybutyl)nitrosamines. The essential structural and metabolic requirements in N-nitrosamines for the induction of bladder cancer in the rat are discussed. (Author abstract) (25 Refs)

3. METABOLIC FATE OF N-BUTYL-N-(4-HYDROXYBUTYL)NITROSAMINE AND N,N-DIBUTYLNITROSAMINE IN THE GUINEA PIG, WITH REFERENCE TO THEIR CARCINOGENIC EFFECTS ON THE URINARY BLADDER.

Suzuki E, Aoki J, Okada M
Tokyo Biochemical Res. Inst., Takada 3-41-8, Toshima-ku, Tokyo 171, Japan

Gan; 72(4):547-551 1981

The metabolic fate of two urinary bladder carcinogens, N-butyl-N-(4-hydroxybutyl)nitrosamine(BBN) and N,N-dibutylnitrosamine (DBN), was studied in the guinea pig, in order to elucidate species differences of response to these N-nitrosamines in this animal species and the rat. Based on the urinary metabolites characterized after oral administration of these compounds, the metabolic pathways of BBN and DBN in the guinea pig were shown to be essentially similar to those in the rat. The principal urinary metabolite of BBN and DBN in the guinea pig, however, was not N-butyl-N-(3-carboxypropyl)nitrosamine (BCPN), as was the case in the rat, but the glucuronic acid conjugate of BBN and that of N-butyl-N-(3-hydroxybutyl)nitrosamine, respectively. The species variation in response to BBN and DBN as bladder carcinogens in these animals is discussed on the basis of the urinary excretion of BCPN. (Author abstract) (27 Refs)

4. SALIVARY LEVELS OF N-NITROSAMINES AND SOME METABOLITES AFTER IP INJECTION OF N-NITROSAMINES IN RATS.

Fliessbach JH, Guttenplan JB
Dept. Biochemistry, New York Univ. Dental Center, New York, NY, 10010

Res Commun Chem Pathol Pharmacol; 33(2):283-291 1981

The carcinogens N-nitrosodimethylamine (DMN) and N-nitrosodiethylamine (DEN) were detected in rat saliva by gas liquid chromatography or HPLC after their ip injections. Salivary levels were equal to or greater than blood levels. A fairly linear dose response in salivary levels was observed in the range of 1-50 mg/kg. Salivary levels of DMN and DEN decreased between 0.5 and 1.0 hr after administration with the decrease becoming more prominent at lower doses. Formaldehyde and bicarbonate, metabolites of DMN, were also detected in rat saliva. (Author abstract) (19 Refs)

5. MASS SPECTROMETRY OF 2-SUBSTITUTED 5-NITRO-2-FURYL THIAZOLES. IDENTIFICATION OF MICROSOMAL NITROREDUCTION PRODUCTS BY ELECTRON IMPACT MASS SPECTROMETRY.

Mattammal MB, Zenser TV, Davis BB
St. Louis Veterans Admin. Medical Center, Geratric Res., Education and Clinical Center, St. Louis, MO, 63125

Biomed Mass Spectrom; 8(7):305-311 1981

The electron impact mass spectral fragmentation of nitro heterocyclic carcinogens N-[4-(5-nitro-2-furyl)-2-thiazolyl]formamide, 2-amino-4-(5-nitro-2-furyl)thiazole, 2-methyl-4-(5-nitro-2-furyl)thiazole and 2-methylamino-4-(5-nitro-2-furyl)thiazole were studied. The molecular ions undergo two modes of cleavage: one giving [M-84]+ ions which include the 2-substituted thiazole ring, while the other gives rise to the fragment [M-74]+ ions. The products of anaerobic microsomal nitroreduction of 2-methyl-4-(5-nitro-2-furyl)thiazole were isolated and purified by high-pressure liquid chromatography. The metabolites undergo different fragmentation patterns compared to the parent nitro analogs. Metabolites from anaerobic enzymatic reduction showed identical gas chromatographic, high-pressure liquid chromatographic and thin-layer chromatographic properties to the chemically synthesized material. The metabolites were identified as 1-(2-methyl-4-thiazolyl)-3-cyano-1-propenone and 1-(2-methyl-4-thiazolyl)-3-cyano-1-propanone by mass spectral fragmentation pattern. (Author abstract) (22 Refs)

6. CHLOROETHANES: THEIR METABOLISM BY HEPATIC CYTOCHROME P-450 IN VITRO.

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Dept. Medical Biochemistry, Univ. Cape Town Medical Sch., Observatory 7925 Cape, South Africa
Carcinogenesis; 2(8):697-702 1981

Hepatic Microsomes were obtained from male Long-Evans rats. Microsome suspensions were exposed to 1,1,1-trichloroethane (111T), 1,1,2-trichloroethane (112T), or 1,1,2,2-tetrachloroethane (1122T). Levels of cytochrome P450 were measured, and metabolites of the chloroethanes were identified and quantified. The binding of chloroethanes was enhanced by the induction of cytochrome P-450 by phenobarbital (PB). It was not enhanced by the induction of cytochrome P-448 by beta-naphthoflavone (BNF). All three chloroethanes stimulated CO-inhibitable NADPH oxidation (CINO) by the hepatic microsomes. BNF induction decreased CINO for all three chloroethanes. PB induction increased CINO for 111T and 112T, but not for 1122T. CINO and metabolite formation were inhibited by CO, 2-diethylaminoethyl-2,2-diphenylvalerate (SKF-525A), and/or metyrapone. The results confirmed that all three chloroethanes were metabolized by cytochrome P-450. The metabolites of 111T, 112T, and 1122T were 2,2,2-trichloroethanol, monochloroacetate, and dichloroacetate, respectively. Proposed mechanisms for metabolism are described, with relationship to the relative mutagenicity and carcinogenicity of the three chloroethanes. (29 Refs)

OTHER METABOLISM OF CARCINOGENS

7. RELEASE OF MUTAGENIC METABOLITES OF BENZO[A]PYRENE FROM THE PERFUSED RAT LIVER AFTER INHIBITION OF GLUCURONIDATION AND SULFATION BY SALICYLAMIDE.

Bock KW, Bock-Hennig BS, Lilienblum W, Volp RF
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Chem Biol Interact; 36(2):167-177 1981

The role of glucuronide and sulfate conjugation in presystemic inactivation of benzo[a]pyrene (BP) metabolites was investigated with rat livers perfused with BP (12 u moles). Comparisons were made between metabolite profiles and mutagenicity of medium from perfusions with and without salicyclamide, a selective inhibitor of glucuronide and sulfate conjugation. After 4 hr perfusion in the presence of salicylamide, certain BP metabolites (diols, quinones, phenols, and metabolites more polar than BP-9,10-diol) were significantly increased at the expense of quinones and phenols in the glucuronide fraction. Mutagenicity of medium (detected by the Ames test, using tester strains TA98 and TA100) was low in perfusion without salicylamide. Mutagenicity detected with tester strain TA98 was significantly increased in perfusions with salicylamide. Involvement of glucuronidation in BP inactivation was also observed at the subcellular level when cofactors of glucuronidation were added to liver homogenates along with the NADPH regenerating system in the Ames test, BP mutagenicity was markedly decreased. Both the activation of BP to mutagenic metabolites and the inactivation of BP metabolites by glucuronidation was much more pronounced with liver homogenates from 3-methyl-cholanthrene-treated rats than with those from phenobarbital-treated animals or untreated controls. The results suggest an important role for glucuronidation and sulfation in the inactivation and elimination of polycyclic aromatic hydrocarbons. (Author abstract) (26 Refs)

8. GLUCURONIC ACID CONJUGATES OF METABOLITES OF 7,12-DIMETHYLBENZ(A)ANTHRACENE EXCRETED THROUGH BILE DUCTS IN RAT.

Khanduja KL, Dogra SC, Sharma RR

Dept. Biophysics, Postgraduate Inst. Medical Education and Res., Chandigarh 160 012, India

Indian J Exp Biol; 19(4):375-378 1981

The nature of metabolites of 7,12-dimethylbenz(a)anthracene (DMBA) excreted through the biliary ducts of female Wistar rats was examined through thin layer and column chromatography. The results indicated that diols or dihydrodiols and not phenols of DMBA could be the main metabolites which conjugate with glucuronic acid for rapid excretion of the carcinogen in the bile. (24 Refs)

9. METABOLIC FATE OF N,N-DIPROPYLNITROSAMINE AND N,N-DIAMYLNITROSAMINE IN THE RAT, IN RELATION TO THEIR LACK OF CARCINOGENIC EFFECT ON THE URINARY BLADDER.

Suzuki E, Okada M

Tokyo Biochemical Res. Inst., Takada 3-41-8, Toshima-ku, Tokyo 171, Japan

Gan; 72(4):552-561 1981

The metabolic fate of N,N-dipropylnitrosamine (DPN) and N,N-dipentyl(=diamyl)nitrosamine (DAN), which induce tumors principally in the liver and esophagus but not in the urinary bladder, was studied in the rat, in order to elucidate the reason for this lack of carcinogenicity to the urinary bladder in contrast with the butyl homolog, N,N-dibutylnitrosamine (DBN), a potent bladder carcinogen. The principal urinary metabolite of DPN was identified as the omega-oxidation product N-propyl-N-(2-carboxyethyl)nitrosamine. The (omega-1)-oxidation product N-propyl-N-(2-hydroxypropyl)nitrosamine and its glucuronic acid conjugate were also characterized as metabolites. The principal urinary metabolite of DAN was N-amyl-N-(2-carboxyethyl)nitrosamine, which was formed by metabolic shortening of the amyl chain by omega- and beta-oxidations according to the Knoop mechanism. Besides this, seven compounds oxidized at omega-, (omega-1)-, (omega-2)-, and (omega-3)-positions of one or both amyl chains were isolated and characterized, some of which were shown to be also present as the corresponding glucuronide. The metabolic pattern of DPN and DAN was compared with that of DBN, and the lack of carcinogenicity of the former N-nitrosamines to the urinary bladder of rats is discussed on the basis of their urinary metabolites. (Author abstract) (20 Refs)

MODIFICATION OF CARCINOGEN METABOLISM

10. THE IMPORTANCE OF SHORT TERM EXPOSURE OF C3H 10T1/2 CELLS TO POLYCYCLIC HYDROCARBONS: EVIDENCE FOR HYDROCARBON-MEDIATED ANTICARCINOGENIC ACTIVITY.

Sarrif AM, Strobel-Stevens J, Miller C, Smythies JR
Dept. Pharmacology, Univ. Alabama in Birmingham Medical Center, Birmingham, AL, 35255
Cancer Lett; 13(4):291-297 1981

The effects of short term exposure of C3H 10T1/2 mouse embryo cells to benzo[a]pyrene (BP) and 3-methylcholanthrene (3-MC) were studied. Within the concentration range of 0.3 to 10 ug/ml, increasing the time of exposure from 15 min to 24 hr did not alter cytotoxicity (as determined by plating efficiency) appreciably; cell survival ranged between 70-90% of control. For both carcinogens, transformed foci were observed in as little as 15 min. Between 0.3-1.25 ug/ml BP, transformation frequency (TF) (the number of transformed foci/1,000 surviving cells) increased with time of exposure; at concentrations between 2.5-10 ug/ml a max TF of 2 was observed for cells exposed to BP for 3 hr. Exposure to high concentrations of 3-MC produced an optimal TF after 30 min to 1 hr. The dependency of TF on BP or 3-MC concentration at selected times was profiled. One hr exposure produced a TF which increased with increasing concentrations. After BP exposure for 3 hr, TF reached a max of 2 at 5 ug/ml; after 6 hr TF peaked at 1.25 ug/ml and decreased at higher concentrations. Results with 3-MC differed: with a 3 hr incubation TF peaked at 1.25 ug/ml and at 24 hr 0.625 ug/ml caused max TF. The changes observed in TF were not likely to result from toxic effects. In this study the transformation of 10T1/2 cells by BP and 3-MC depended upon both concentration and time of exposure. Since both BP and 3-MC are extensively metabolized to polyoxygenated derivatives and conjugates, certain of the metabolites may have acted as antipromoting agents. (21 Refs)

11. EFFECT OF GLUTATHIONE AND URIDINE 5'-DIPHOSPHOGLUCURONIC ACID ON MUTAGENESIS BY BENZO[A]PYRENE AND AFLATOXIN B1 IN THE SALMONELLA/MICROSOME ASSAY.

Malaveille C, Brun G, Hautefeuille A, Bartsch H
Programme of Environmental Carcinogens and Host Factors, Div. Chemical and Biological Carcinogenesis, International Agency for Res. on Cancer, 150 cours Albert-Thomas, F-69372 Lyon Cedex 2, France
Mutat Res; 83(1):15-24 1981

The role of the conjugating enzymes, glutathione-S-transferase (GSH-S-T) and uridine 5'-diphosphoglucuronic acid (UDPGA) on rat liver S9-mediated mutagenesis of benzo(a)pyrene (BP) and aflatoxin B1 (AFB) in the Salmonella/microsome assay was investigated. In S typhimurium TA100, the UDPGA-dependent reduction of BP mutagenicity was related to the liver S9 concentration: max reduction (40%) in mutagenicity was noted with an S9 concentration of 50 ul/plate. In liquid assays, the presence of 2.5 milliM UDPGA for 20 min caused a two-fold increase in BP mutagenicity at a concentration of 40 uM BP. At 20 uM BP, the presence of UDPGA either did not change or decreased mutagenicity of BP; after 30 min of incubation, a significant decrease was observed. With 20 and 40 uM BP, the addition of GSH to the assays decreased BP mutagenesis by 1.8-and 1.5-fold in the presence of 17% and 9% (vol/vol) liver S9, respectively. GSH had no effect at two-fold lower concentrations of BP. The effect of glutathione (GSH) on AFB mutagenesis was dependent on its concentration. AFB mutagenicity decreased at concentrations of AFB greater than 7.5 nanoM; at 30 nanoM AFB, the AFB mutagenesis was reduced by 1.8-fold. In liquid assays, in the presence of 4.4% S9 from untreated rats the addition of 10 milliM GSH changed the AFB mutagenesis only at concentrations greater than 100 nanoM, resulting in an enhancement of AFB mutagenicity. (43 Refs)

12. PROMOTIVE EFFECTS OF DEOXYCHOLIC ACID ON HEPATOCARCINOGENESIS INITIATED BY DIETHYLNITROSAMINE IN MALE RATS.

Cameron R, Imaida K, Ito N
First Dept. Pathology, Nagoya City Univ. Medical Sch., 1 Kawasumi, Mizuho-cho, Mizuho-ku, Nagoya 467, Japan
Gan; 72(4):635-636 1981

The ability of deoxycholic acid (DA), administered over a short time period, to promote the appearance of hyperplastic foci or hyperplastic nodules in diethylnitrosamine (DEN)-initiated male Fischer rats was examined. The 80 rats were divided into five groups, 15 rats in Groups 1-4 and 20 rats in Group 5. Groups 1, 3, and 5 were injected ip with DEN and later Groups 1 and 3 were fed 0.5% DA or 0.05% phenobarbital (PB), respectively, for 10 wk. Groups 2 and 4 were given saline in place of DEN and later fed DA or PB alone for 10 wk. Both DA and PB (Groups 1 and 3) promoted the development of considerable numbers of foci positive for gamma-glutamyl transferase if preceded by DEN initiation. DEN alone (Group 5) induced much fewer and relatively small foci but induced no hyperplastic nodules. Significantly more and larger foci and a considerably greater number of hyperplastic nodules were seen with DA (Group 1) than with PB (Group 3). DA without DEN (Group 2) induced a small number of foci and hyperplastic nodules. These data suggested that DA is a moderately strong promoter of preneoplastic liver lesions in the male rat. (9 Refs)

13. EFFECT OF PRETREATMENT WITH PREGNENOLONE-16ALPHA-CARBONITRILE AND PROTEIN-FREE DIET ON THE METABOLISM AND CARCINOGENICITY OF DIMETHYLNITROSAMINE.

Kiessling M, Lipinski R, Bohm N, Kleihues P
Pathologische Institut, Universitat Freiburg, 78 Freiburg, W. Germany
Carcinogenesis; 2(8):757-761 1981

Adult female Wistar rats were pretreated with a protein-free diet (PFD), pregnenolone-16alpha-carbonitrile (PCN: total dose 25 mg, 5 equal doses at 12-hr intervals), or a combination of both. Rats from each group were given a single injection of 60 mg dimethylnitrosamine (DMN). PCN-pretreated rats showed a 50% tumor incidence after a mean survival time of 672 days. PFD (30 rats) and PFD + PCN (28 rats) groups showed a tumor incidence of 83-85% and a mean survival time of 357 and 396 days. Rats treated only with PCN showed a tumor incidence of 50% with a mean survival time of 805 days. The incidence of neoplasms, particularly cholangiomas, was highest following treatment with PCN only. The PFD and PFD + PCN groups showed lower incidence of cystic cholangiomas and no malignant liver tumors. Methylation of liver DNA purines by a single dose of [14C] DMN was greatest in the PCN and PFD groups and lower in the PFD + PCN group. Methylation of renal DNA was highest in the PFD and PFD + PCN groups and lower in the PCN-only pretreated group. Differences in lung tissue were smaller among the various groups. Both PCN and PFD reduced the hepatotoxicity of DMN. PCN had no effect on the induction of renal tumors. Apparently PCN does not cause a reduction in DNM metabolism in the liver and the resultant increase in DNA methylation in the kidney. PFD shifts the metabolism of DMN from the liver to the kidney, lowering the carcinogenic effect of DMN in the liver and raising it in the kidney. (24 Refs)

14. EFFECTS OF HARMAN AND NORHARMAN ON THE METABOLISM OF ANILINE AND P-DIMETHYLAMINOAZOBENZENE.

Hayashi K

Dept. Public Health, Jikei Univ. Sch. Medicine, Tokyo, Japan

Nippon Eiseigaku Zasshi; 36(2):495-505 1981

The metabolism and mutagenicity of aniline and p-dimethylaminoazobenzene (p-DAB) were studied in vitro using rat liver microsomes. In the absence of harman (l-methyl-9H-pyrido[3,4-b]indole) and norharman (9H-pyrido[3,4-b]indole), p-DAB was metabolized to aniline without accumulation of p-methylaminoazobenzene (p-MAB) or p-aminoazobenzene (p-AAB). Aniline was metabolized to p-aminophenol (p-AP). Harman or norharman substantially inhibited metabolism of aniline to p-AP in microsomes. Norharman was a greater inhibitor than harman. Norharman slightly reduced the metabolism of p-DAB to aniline and caused the accumulation of p-DAB, p-MAB, and p-AAB. The metabolites of aniline, o-aminophenol, m-aminophenol, p-AP, and nitrosobenzene, were tested for mutagenicity in Salmonella typhimurium TA98. Nitrosobenzene was mutagenic only in the presence of norharman with S-9 mix. Similarly p-MAB, p-AAB, and aniline were mutagenic in TA 98 only in the presence of norharman with S-9 mix. Harman and norharman each greatly inhibited aniline hydroxylase activity, while aminopyrene demethylase had only a slight effect. Aryl hydrocarbon hydroxylase was inhibited by norharman, but not by harman. (23 Refs) (In JPN)

15. NITRITE CONVERTS 2-AMINO-ALPHA-CARBOLINE, AN INDIRECT MUTAGEN, INTO 2-HYDROXY-ALPHA-CARBOLINE, A NON-MUTAGEN, AND 2-HYDROXY-3-NITROSO-ALPHA-CARBOLINE, A DIRECT MUTAGEN.

Tsuda M, Nagao M, Hirayama T, Sugimura T

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Mutat Res; 83(1):61-68 1981

The conversion of 2-amino-alpha-carboline (AAC), a mutagen isolated from the pyrolysate of soybean globulin, into a non-mutagenic hydroxy derivative and then into a new mutagen by treatment with nitrite under acidic conditions is reported. AAC was mutagenic to Salmonella typhimurium in the presence of a rat-liver microsomal fraction (S9 mix): 25 nanomoles of AAC induced 1,156 and 108 revertants of TA98 and TA100, respectively, with S9 mix, and no revertants without S9 mix. Incubation with nitrite under acidic conditions decreased or abolished the mutagenicity with S9 mix. However, below pH 3, mutagenicity that did not require S9 mix appeared. This direct acting mutagen was found to be 2-hydroxy-3-nitroso-alpha-carboline (HNAC) by mass and proton magnetic resonance spectroscopy. It was shown that AAC was converted into 2-hydroxy-alpha-carboline which was then converted into HNAC. The physiological significance of these findings are discussed. (30 Refs)

16. MODIFICATION OF THE MUTAGENICITY AND TERATOGENICITY OF CYCLOPHOSPHAMIDE IN RATS WITH INDUCERS OF THE CYTOCHROMES P-450.

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Teratology; 24(1):1-11 1981

The chemotherapeutic agent cyclophosphamide (CP) may act as a carcinogen if it is enzymatically metabolized to reactive intermediates with alkylating, mutagenic, or cytotoxic effects, which activation is thought to be catalyzed by the cytochrome P-450 monooxygenase system. Phenobarbital (PB) induces the hepatic cytochrome P-450 that is involved in the activation of CP to both alkylating and mutagenic metabolites; beta-naphthoflavone (bNF) induces a different cytochrome P-450 and actually decreases the activation of CP by liver microsomes. Using rats pretreated with either PB or bNF, the activation of CP to mutagenic metabolites by enzyme fractions on day 13 of gestation was measured with the Ames test on Salmonella typhimurium TA1535 and teratogenicity was assessed in vivo by treatment of rats with CP on day 13 of gestation. CP was activated to mutagenic metabolites to the same extent (on a tissue wet wt basis) by enzyme fractions from maternal liver, kidney, and placenta, despite differences in cytochrome P-450 content, but fetal homogenates did not activate CP. PB pretreatment increased the liver cytochrome P-450 content 1.8-fold and the activation of CP by maternal liver microsomes 10-fold; however, PB did not alter the activation of CP by maternal kidney, by placenta, or by the fetus. PB pretreatment increased the teratogenicity of CP as measured by an increased incidence of malformed embryos or by decreased fetal wt. Pretreatment with bNF did not induce the hepatic cytochrome P-450 in the pregnant rat; did not change the activation of CP to mutagenic metabolites by liver, kidney, the placenta, or the fetus; and had no effect or decreased the teratogenicity of CP. These results suggest that the mother, rather than the fetus, is the site of PB activation; that the principal site of activation is the maternal liver; and that there is a correlation between the teratogenicity and mutagenicity of CP after induction by cytochrome P-450. (36 Refs)

17. EFFECTS OF 2-AND 3-TERT-BUTYL-4-HYDROXYANISOLE ON GLUTATHIONE S-TRANSFERASE AND EPOXIDE HYDROLASE ACTIVITIES AND SULFHYDRYL LEVELS IN LIVER AND FORESTOMACH OF MICE.

Lam LK, Sparnins VL, Hochalter JB, Wattenberg LW

Dept. Lab. Medicine and Pathology, Univ. Minnesota, Minneapolis, MN, 55455

Cancer Res; 41(10):3940-3943 1981

Butylated hydroxyanisole, a food additive, has been found to inhibit the neoplastic effects of a wide variety of chemical carcinogens. The commercially available preparations of butylated hydroxyanisole contain two isomers, 2-tert-butyl-4-hydroxyanisole (2-BHA) and 3-tert-butyl-4-hydroxyanisole (3-BHA). Both isomers induce increased activities of glutathione (GSH) S-transferase and epoxide hydrolase and increase acid-soluble sulfhydryl concentration in hepatic and forestomach tissues of A/HeJ mice. The inductions were assayed after 2 wk of feeding diets containing the two isomers. 3-BHA induced an increase in the activity of hepatic microsomal epoxide hydrolase by 1.4x that of the control. The activity of cytosol GSH S-transferase was enhanced by both isomers. In the liver, the 3-BHA induction was more than 3x higher than that of 2-BHA. In the forestomach, however, the induction effect of the two isomers was reversed. The overall magnitude of the induction was much lower in the forestomach than in the liver. Synergistic effects on the induction of GSH S-transferase activity were observed in the forestomach cytosol when mixtures of different proportions of the two isomers were added to the diet. Max enzyme activity was obtained at a ratio of 75% 2-BHA and 25% 3-BHA. No synergistic effect was observed with the corresponding hepatic cytosolic enzyme. The relative inductive effects of 2-and 3-BHA on the acid-soluble sulfhydryl level of liver and forestomach tissues followed closely those on GSH S-transferase activity. The results of the present study show that the two isomers of butylated hydroxyanisole differ in the magnitude of their effects on carcinogen-metabolizing systems of the liver and forestomach. (Author abstract) (27 Refs)

MUTAGENICITY OF ACTIVATED METABOLITES OF CARCINOGENS

18. FRAMESHIFT MUTATIONS: RELATIVE ROLES OF SIMPLE INTERCALATION AND OF ADDUCT FORMATION.

McCoy EC, Rosenkranz EJ, Petrullo LA, Rosenkranz HS
Center for Environmental Health Sciences, Sch. Medicine, Case Western Reserve Univ., Cleveland, OH, 44106
Mutat Res; 90(1):21-30 1981

The mutagenic properties of 9-aminoacridine, its derivative quinacrine, and the nitro-containing derivative Entozon were examined in Salmonella typhimurium and Escherichia coli WP2uvrA assays. Both 9-aminoacridine and quinacrine induced frameshift mutations in strain TA1537 only (with, respectively, 1.7 and 3.0 revertants/nanomole (r/nm)), confirming the finding that simple intercalators mutate this strain alone. Entozon primarily affected strains TA98 (338 r/nm) and TA1538 (288 r/nm), indicators for frameshift mutations resulting from adduct formation; mutagenicity was greatly decreased when Entozon was tested in strain TA1978 (23 r/nm), the uvrB+ analog of TA1538 which does not respond maximally to the mutagenic action of adduct-forming chemicals as a result of its intact uvrB system. Entozon displayed no base-substitution activity for Salmonella, although it exhibited some activity when tested in E coli WP2uvrA (2.4 r/nm). When a cell is exposed to a molecule inducing frameshift mutations by intercalation and adduct formation, the formation of adducts apparently exerts a much stronger influence on total mutagenic expression. (47 Refs)

19. RAT HEPATOCYTE-MEDIATED MUTAGENESIS OF HUMAN CELLS BY CARCINOGENIC POLYCYCLIC AROMATIC HYDROCARBONS BUT NOT ORGANOCHLORINE PESTICIDES.

Tong C, Fazio M, Williams GM
Naylor Dana Inst. for Disease Prevention, American Health Foundation, Valhalla, NY, 10595
Proc Soc Exp Biol Med; 167(4):572-575 1981

The establishment of a hepatocyte primary culture-mediated human cell hypoxanthine-guanine phosphoribosyl transferase (HGPRT) mutagenesis assay is reported. In the rat hepatocyte primary cultures (HPC)-mediated Detroit 550 (D-550) HGPRT mutation assay, 1 x 10(6) D-550 were generally coplated with 20 x 10(6) freshly prepared HPC. The cocultures were allowed to attach for 2 hr, were washed, and fresh media containing the carcinogens or appropriate controls were added for 24 hr exposure. The cultures were washed then allowed to grow for 10 days to allow mutant expression. In general, by day 4, no viable HPC were observed. HGPRT mutants were selected in the human foreskin cell line D-550 by 6-thioguanine (TG). Exposure of D-550 alone to benzo(a)pyrene or 7,12-dimethylbenz(a)anthracene did not result in any increase in TG-resistant (TGr) mutant incidence over the parallel-run control. However, a significant increase in the TGr mutant incidence over that in control cultures occurred in D-550 when the carcinogen exposure was in the presence of HPC. With dichlorodiphenyltrichloroethane, chlordane, and mirex, no significant increase in TGr mutant incidence was observed in the exposed human cells either in the presence or absence of HPC. An epigenetic mechanism for the carcinogenicity of these organochlorine pesticides is suggested. (34 Refs)

20. NITRATED FLUORENE DERIVATIVES ARE POTENT FRAMESHIFT MUTAGENS.

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Center for Environmental Health Sciences, Sch. Medicine, Case Western Reserve Univ., Cleveland, OH, 44106
Mutat Res; 90(1):11-20 1981

The structure-activity relationship of polynitrated polycyclic aromatic hydrocarbons (PAH) which might be present in the environment as a result of incomplete combustion and subsequent nitration by oxides of nitrogen was investigated. The biological activity of 2-nitrofluorene, 2,7-dinitrofluorene, 2,7-diaminofluorene, (2,4,7-trinitro-9-fluorenylidene) malononitrile, 2,4,5,7-tetranitro-9-fluorenone, 2,7-dinitro-9-fluorenone, and 2,4,7-trinitro-9-fluorenone was studied. Significant mutagenic activity was observed for all the compounds in Salmonella typhimurium strains TA1538, TA98, and TA1537; a corresponding lack of activity or only minimal activity was observed in strain TA1535 and in Escherichia coli WP2 uvrA, indicating a frameshift type of mutagenicity. Mutagenic action is based on a reduction of the nitro-function to the corresponding hydroxylamines, the penultimate mutagens, which following esterification to electrophiles apparently react with the guanine moiety of DNA to form adducts. Max mutagenic activity was observed with the trinitro-substituted compound; addition of a fourth nitro group resulted in diminished activity, presumably reflecting steric hindrance of either enzyme reduction of the nitro-function or of DNA-adduct formation. (45 Refs)

21. MUTAGENICITY OF N-ALKYL-N-(ALPHA-ACETOXYALKYL)NITROSAMINES IN V79 CHINESE HAMSTER CELLS IN RELATION TO ALKYLATING ACTIVITY.

Huang GF, Mochizuki M, Anjo T, Okada M
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Gan; 72(4):531-538 1981

Mutation to ouabain resistance and cytotoxicity were tested in V79 Chinese hamster cells after the cells had been treated for 2.5 hr with a series of N,N-dialkylnitrosamines (alkyl=methyl, ethyl, propyl, butyl or tert-butyl) monosubstituted at the alpha-carbon with an acetoxy group. The effects of the length of alkyl chain and the mode of substitution with the acetoxy group on the cytoxicity and mutagenicity were examined. In the series of N-alkyl-N-(acetoxymethyl)nitrosamines with an acetoxy group at the primary alpha-carbon, the methylating compound N-methyl-N-(acetoxymethyl)nitrosamine was the most cytotoxic and mutagenic, and the biological activities decreased in the order of ethyl, butyl and propyl homologs. N-tert-Butyl-N-(acetoxymethyl)nitrosamine was not mutagenic at the concentration tested. At equitoxic concentration, N-ethyl-N-(acetoxymethyl)nitrosamine was found to be the most mutagenic. Of the two N-alkyl-N-(alpha-acetoxybutyl)nitrosamines having an acetoxy group at the secondary alpha-carbon, N-methyl-N-(alpha-acetoxybutyl)nitrosamine was more cytotoxic and mutagenic than N-butyl-N-(alpha-acetoxybutyl)nitrosamine. A comparison of the corresponding N-alkyl-N-(acetoxymethyl)nitrosamines and N-alkyl-N-(alpha-acetoxybutyl)nitrosamines showed that the latter had stronger activities. A plot of the mutation frequency versus the ability of the alpha-acetoxy compounds to alkylate 4-(p-nitrobenzyl)pyridine was linear. This indicates that the chemical reactivity of the compounds plays an important role in inducing mutation in V79 Chinese hamster cells. (Author abstract) (26 Refs)

22. MUTAGENICITY OF REACTION PRODUCTS OF SULPYRINE WITH NITRITE.

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Mutat Res; 90(1):57-65 1981

The mutagenicity of three N-nitroso products of sulpyrine (1-diketobutyryl-1-phenyl-2-methyl-2-nitrosohydrazide hydrate (DPMN), 4-(N-methyl-N-nitroso)aminoantipyrine (MNAA), and 1-acetyl-1-methyl-2-nitroso-2-phenylhydrazine) and of related compounds (4-methylaminoantipyrine, 1-acetyl-1-methyl-2-phenylhydrazine, 4-hydroxyantipyrine, sulpyrine, and sodium nitrite) was tested on Salmonella typhimurium TA100 and TA98. DPMN, MNAA, and sodium nitrite were mutagenic to TA100 but not to TA98. None of the other compounds were mutagenic to either strain. Activation of mutagenicity with rat-liver microsomal preparation (S9 mix) was required by MNAA, but not by DPMN. The addition of L-cysteine or glutathione markedly increased the mutagenicity of DPMN; the enhancing effects were proportional to concentration added. The possibility that sulpyrine might pose a carcinogenic hazard in man is discussed. (25 Refs)

23. MUTAGENICITY OF AMIDE TYPE AND CARBAMATE TYPE DIAZOALKANE-GENERATING AGENTS IN SALMONELLA/MICROSOME ASSAY.

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Chem Pharm Bull (Tokyo); 29(6):1758-1762 1981

Both amide type and carbamate type N-nitroso compounds, which have a common structure and have been reported to be excellent diazoalkane-generating compounds were examined for mutagenicity by measuring their ability to create histidine (his) prototrophic revertants of two his-dependent Salmonella typhimurium strains: T100 (a base-pair substitution strain) and TA98 (a frameshift strain), with and without metabolic activation by S-9 mix. Six compounds of each type having systematic substitutions at two different sites of the basic common structure were examined systematically over dose ranges of 0.27-2.7 umole (4 x 10(-5) to 4 x 10(-2) M). In the absence of activation, none of the amide type compounds showed any mutagenicity in either strain. With metabolic activation, two of six amide type compounds (both having a benzyl group in the same position) were weakly mutagenic to TA100. In the absence of S-9 mix, only one of six carbamate type compounds showed any mutagenicity (against TA98); in the presence of S-9 mix, all six carbamate compounds were mutagenic against TA100 over a wide range of concentrations and two of six were weakly mutagenic against TA98. There is apparently a structure-mutagenicity relationship for amide type and carbamate type compounds that is principally dependent upon the rate of chemical generation of diazoalkane or phenyldiazomethane in alkaline soln. (8 Refs)

24. SPECIES DIFFERENCE IN LIVER MICROSOMAL AND CYTOSOLIC ENZYMES INVOLVED IN MUTAGENIC ACTIVATION OF N-HYDROXY-N-2-FLUORENYLACETAMIDE.

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JNCI; 67(3):549-555 1981

The mutagenic activations of N-hydroxy-N-2-fluorenylacetamide (N-OH-2-FAA) by subcellular fractions of the livers of rat, the mouse, guinea pig, hamster and monkey were examined for sensitivity to paraoxon, which inhibits a deacetylase but not an arylhydroxamic acid acyltransferase. The mutagenic activation by liver microsomes was almost entirely mediated by a paraoxon-sensitive enzyme in all the animals tested. In contrast the mutagenic activation by liver cytosol was mediated mostly by a paraoxon-sensitive enzyme in mice and guinea pigs, mostly by a paraoxon-resistant enzyme in rats and hamsters, and by both enzyme types in the monkey. In rats and guinea pigs, attempts were made to identify the enzymes causing mutagenic activation in the liver cytosol by a comparison of the elution positions of these enzymes in gel filtration and DEAE-cellulose column chromatography with those of known enzymes. In the rat liver cytosol, the mutagenic activation was mediated not only by acyltransferase but also by an unknown enzyme, which was resistant to paraoxon and differed from acyltransferase in chromatographic behavior. In the guinea pig liver cytosol, the activation was due to deacetylase activities, which could be separated into four fractions by gel filtration. These data indicate that species differ in the kinds of liver cytosolic enzymes involved in mutagenic activation of N-OH-2-FAA but not in the kind of liver microsomal enzyme involved . (Author abstract) (31 Refs)

25. FRAMESHIFT MUTAGENESIS OF 9-AMINOACRIDINE DERIVATIVES IN SALMONELLA TYPHIMURIUM.

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Mutat Res; 90(1):1-10 1981

A number of 9-aminoacridine derivatives with various substituents on the exocyclic amino group were tested in the absence of activation by rat-liver microsomes in order to determine the effect of the substituents on frameshift activity and specificity. The four acridine derivatives tested were 9-aminoacridine, a spin-labeled 9-aminoacridine derivative (4-(9-acridinylamino)-2,2,6,6-tetramethyl-1 piperidinyloxy), quinacrine dihydrochloride, and the putative bisintercalator N,N'-bis(2-methoxy-6-chloroacridine)-tetraethyl enephetamine pentahydrochloride. Frameshift mutagenesis of the acridines was sequence-specific in that significant activity occurred only with the two strains with a +1 frameshift his C (Salmonella typhimurium strains TA1537 and TA1977) and not with the two strains in which reversion was required at a +2 frameshift in his D (TA1538 and TA1978). Excision repair via uvr B was involved only to a minor extent in the production of a frameshift reversion at the his C locus by the four compounds tested. The dose-response of frameshift reversion at his C induced by the acridine was nonlinear. These results are consistent with a model derived from nuclear magnetic resonance experiments on 9-aminoacridine binding to dinucleoside phosphates, in which the N-H group is situated in the duplex so as to participate in a hydrogen bond with one base while excluding its complementary partner, thereby provoking mismatching. (18 Refs)

26. BACTERIAL MUTAGENICITY AND TOXICITY OF CYCLOALIPHATIC EPOXIDES.

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Mutat Res; 90(1):67-78 1981

The Ames mutagenicity test with Salmonella was used to investigate mutagenicity of 12 cycloaliphatic epoxides without the addition of liver homogenate fractions. Eight compounds exhibited base-pair substitution mutagenic activity. Mutagenicity decreased with expanding ring size, while inhibition of bacterial growth increased with increasing ring size. Epoxide toxicity at the doses required for mutagenicity prevented establishment of meaningful dose-response relationships. Petri dish sealing bands were used to prevent loss of volatile compounds during 48 hr incubation. Mutagenicity was greater in TA1535 than in TA100; toxicity was more pronounced in TA100. Toxicity was not reduced by the use of less permeable strains (TA92, TA1950, and TA2410). Cyclooctane oxide testing with TA1975 (repair-proficient) and TA1535 (repair-deficient) demonstrated that the bacteria were not being killed by damage to DNA, since toxicity was not reduced in TA1975. The results confirm that cis-1,2-disubstituted oxiranes are mutagenic. (26 Refs)

27. CHROMOSOMAL ANALYSIS IN VINYL CHLORIDE EXPOSED WORKERS: COMPARISON OF THE STANDARD TECHNIQUE WITH THE SISTER-CHROMATID EXCHANGE TECHNIQUE.

Anderson D, Richardson CR, Purchase IF, Evans HJ, O'Riordan ML
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Mutat Res; 83(1):137-144 1981

Twenty-one workers exposed to vinyl chloride (VC) and six controls were subjected to conventional chromosomal analysis (CA) and the determination of sister-chromatid exchanges (SCE). In addition, SCE in human lymphocytes were studied before and after exposure to gaseous VC in vitro. These workers had been subjected to studies 18 mo before. In the exposed workers the av of the different types of abnormalities were significantly increased with CA, while only a slight, nonsignificant, increase of SCE was noted in the exposed group compared with the controls. In lymphocyte cultures exposed to VC during G0/early G1, and late G1/early S phase, no increase in SCE was noted without metabolic activation; a marked decrease was noted with activation and this was independent of cell cycle phase. The small increases of SCE in workers were attributed to low exposures rather than the inability of VC to induce SCE in human lymphocytes; the SCE levels could have returned to normal relatively quickly after exposure. It is suggested that SCE analysis might not be of much value after very low chronic chemical exposures, but might be useful during high chronic chemical exposures and during the first few days after acute exposure. (19 Refs)

28. MUTAGENICITY OF QUINDOXIN, ITS METABOLITES, AND TWO SUBSTITUTED QUINOXALINE-DI-N-OXIDES.

Beutin L, Preller E, Kowalski B
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Antimicrob Agents Chemother; 20(3):336-343 1981

The quinoxaline-di-N-oxides carbadox, olaquindox, and quindoxin, which are potent antibacterial agents, were tested for mutagenicity in the Salmonella microsomal system. They all induced base pair substitutions and frameshift mutations in Salmonella, and occurred independently of the presence of rat liver microsomal fraction in the test system. Mutagenicity was dependent on the presence of their N-oxide groups, since quinoxaline, a completely reduced derivative of quindoxin, was not mutagenic, whereas the partially reduced quinoxaline-N-oxide exhibited a lower mutagenic activity than quindoxin. recA and uvrB Salmonella were found to be more susceptible to mutagenic quinoxaline derivatives than wild-type strains. The mutagenicity of quinoxaline-di-N-oxides was enhanced under anaerobic incubation as was the antibacterial activity. These results suggest that both the antibacterial and mutagenic activity of quinoxalin e-di-N-oxides depend upon the same bacterial activation mechanism. (Author abstract) (26 Refs)

29. MUTAGENICITIES OF CARBADOX AND OLAQUINDOX - GROWTH PROMOTERS FOR PIGS.

Yoshimura H, Nakamura M, Koeda T, Yoshikawa K
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Mutat Res; 90(1):49-55 1981

Both carbadox and olaquindox were positive in the Bacillus subtilis rec and in the Salmonella typhimurium uvr repair tests. In the reverse mutation test with S typhimurium TA100 and TA 98, a linear dose-response relationship was observed for both compounds between 0 and 15 ug/plate. Carbadox was more mutagenic than olaquindox and their activities were marked with strain TA100 (respectively, 315.4 vs 46.3 revertants/ug). In the absence of microsomal supernatant (S9), carbadox was approx 6x more mutagenic than olaquindox; in TA100 with S9, the number of revertant colonies decreased to 146.8/ug with carbadox but only to 38.3/ug with olaquindox. S9 incubation inactivated carbadox almost totally after 10 min, whereas olaquindox retained its activity after 20 min. Carbadox required 20 min to be inactivated by a bacterial cytosol mixture; olaquindox was hardly inactivated after 60 min. Carbadox and olaquindox appear to induce frameshift and base-pair substitution mutations as a result of error in the DNA repair process. Significance of the findings is discussed with respect to use of these compounds as growth promoters in pigs. (18 Refs)

30. DETECTION OF MAMMALIAN CELL MUTAGENS IN URINE FROM CARCINOGEN-DOSED MICE.

Amacher DE, Turner GN, Ellis JH
Drug Safety Evaluation Dept., Pfizer Central Res., Groton, CT, 06340
Mutat Res; 90(1):79-90 1981

Urine was collected from male CD-1 mice dosed by oral gavage with either 300 mg/kg 2-aminofluorene (AF), 150 mg/kg cyclophosphamide (CY), or 200 mg/kg lucanthone (LU), and added directly to L5178Y TK+/- mouse lymphoma cultures (heterozygous at the thymidine kinase locus for the induction of trifluorothymidine-resistant (TFT-R) mutants). After 3 hr incubation, urine from the three different groups of rats produced significant, dose-dependent increases in frequency of

TFT-R mutants. When the drugs were tested directly as mutagens in L5178Y TK+/- cells, LU and CY were positive both with and without metabolic activation, but AF required activation. Significant differences in the direct response of Salmonella typhimurium and L5178Y cells to these compounds indicate that the two cell types may not detect the same chemical entities as proximate mutagens. Urinary metabolites of AF, CY, and either the parental molecule or metabolites of LU can readily be detected as mutagens in a mammalian cell assay. (28 Refs)

31. MUTAGENICITY OF CHEMICALS OF INDUSTRIAL AND AGRICULTURAL RELEVANCE IN SALMONELLA , STREPTOMYCES AND ASPERGILLUS.

Principe P, Dogliotti E, Bignami M, Crebelli R, Falcone E, Fabrizi M, Conti G, Comba P
Istituto Superiore di Sanita, Viale Regina Elena 299-00161, Rome, Italy
J Sci Food Agric; 32(8):826-832 1981

Ethylene dibromide (EDB), ethylene dichloride (EDC), propylene dichloride (PDC), allyl alcohol (AA), and sulfallate (S) were tested for their ability to induce reverse mutations (his+ revertants) in Salmonella typhimurium, forward mutations (streptomycin resistance) in Streptomyces coelicolor, and point mutations (8-azaguanine resistance) in Aspergillus nidulans. EDB and S strongly reverted S typhimurium strains TA100 and TA1535;, PDC had a weak effect on these strains; and EDC was weakly active in TA1535 following microsomal activation with rat liver S-9 mix. This mix reduced the mutagenicity of EBD but not that of S. In S coelicolor, EDB was positive only in spot test experiments and S was weakly positive in plate tests; EDC and PDC were inactive in both test systems. In A nidulans, EDB and PCB gave positive responses in the plate and spot tests and S gave a positive response only in the spot test. AA was was not mutagenic in any of the genetic systems. (21 Refs)

32. MUTAGENIC ACTIVITY OF CAFFEINATED AND DECAFFEINATED COFFEE.

Kam JK
Univ. California, Berkeley, CA, 94720
Cancer Detect Prev; 3(2):507-511 1981

Two types of coffee (caffeinated and decaffeinated) were tested for their mutagenicity using bacterial strains using TA98 and TA100 in Ames Salmonella/Microsome test. According to the Ames criteria, both were found to be mutagenic in the absence of S-9. The mutagens did not require liver enzymes to be activated. (Author abstract) (13 Refs)

33. RELATIONSHIP OF THE RAW WATER QUALITY TO MUTAGENS DETECTABLE BY THE AMES SALMONELLA/MICROSOME ASSAY IN A DRINKING-WATER SUPPLY.

Grabow WO, Van Rossum PG, Grabow NA, Denkhaus R
Natl. Inst. Water Res., Council for Scientific and Industrial Res., P. O. Box 395, Pretoria 0001, South Africa
Water Res; 15(9):1037-1043 1981

The relationship of mutagens detectable by the Ames test to other properties of the Parys, South Africa drinking water supply before and after conventional treatment was studied. The raw water intake was from the Vaal River, subject to pollution with partially purified waste water (nonchlorinated) containing high concentrations of mutagens. Information was obtained on mutagen activity, mutagen formation during conventional water treatment, properties of raw water affecting mutagen concentration in the treated water, and the relation of Ames test results to chemical quality parameters. Mutagens formed during treatment consisted mainly of neutral organic compounds inducing frameshift mutations without liver activation. Although no health hazard was inferred, the results make evident the need for surveillance of potential carcinogens in conventionally treated water taken from a polluted source. (33 Refs)

BINDING OF CARCINOGENS AND THEIR METABOLITES TO MACROMOLECULES

34. BINDING OF BENZO(A)PYRENE DERIVATIVES TO SPECIFIC PROTEINS IN NUCLEI OF INTACT HAMSTER EMBRYO CELLS.

MacLeod MC, Kootstra A, Mansfield BK, Slaga TJ, Selkirk JK
Biology Div., Oak Ridge Natl. Lab., Oak Ridge, TN, 37830
Cancer Res; 41(10):4080-4086 1981

In hamster embryo cells incubated for 24 hr with 4 uM [3H] benzo(a)pyrene, a major portion of the nonextractable radioactivity in nuclear preparations copurifies with the protein fraction. When these proteins are analyzed by sodium dodecyl sulfate:polyacrylamide gel electrophoresis, significant variations in the labeling intensities of the various proteins are seen. Control experiments demonstrate that the labeling is due to covalent binding to protein. Histones H3 and H2A are heavily labeled while the other histones of the nucleosome core, H2B and H4, are devoid of radioactivity. Large amounts of label are associated with proteins with mobilities similar to the very lysine-rich histone H1. However, the results of differential extraction experiments suggest that the labeled proteins do not belong to either the H1 or the high-mobility-group class of chromosomal proteins. During 6 hr of inhibition of protein synthesis by cycloheximide, the metabolism of [3H]benzo(a)pyrene, as monitored by high-pressure liquid chromatography, remained normal. Patterns of labeling of nuclear proteins after 3 or 6 hr were identical in the presence and absence of cycloheximide. This finding strongly suggests that binding of benzo(a)pyrene derivatives to nuclear proteins occurs in situ. (Author abstract) (55 Refs)

35. THE FORMATION AND PERSISTENCE OF BENZO(A)PYRENE METABOLITE-DEOXYRIBONUCLEOSIDE ADDUCTS IN RAT SKIN IN VIVO.

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Int J Cancer; 28(3):387-392 1981

The extent of reaction of benzo(a)pyrene with DNA and the formation of benzo(a)pyrene-deoxyribonucleoside adducts in the skins of male Wistar rats were investigated. Following topical application of benzo(a)pyrene (200 nmoles), binding reached a max of 0.74 pmoles/mg DNA, 12 hr after treatment, and remained high up to 48 hr after treatment. Hydrolysis of the DNA and analysis of the deoxyribonucleoside adducts by HPLC revealed several products. The major adduct, C, (27-40% of the total adducts), co-chromatographed with deoxyribonucleoside adducts formed by reaction of (+-)7beta, 8alpha-dihydroxy-9alpha, 10alpha-epoxy-7,8,9,10-

tetrahydrobenzo(a)pyrene (anti BPDE) with DNA, whilst product B, (19-23% of the total adducts), also formed in significant amounts, co-chromatographed with a further metabolite of 9-hydroxybenzo(a)pyrene bound to an as yet undetermined base in the DNA. Smaller amounts of other deoxyribonucleoside adducts, D and I, were also observed and co-chromatographed with marker compounds derived from reaction of anti BPDE with deoxyadenosine and (+-)7beta, 8alpha-dihydroxy-9beta, 10beta-epoxy-7,8,9,10-tetrahydrobenzo(a)pyrene (Syn BPDE) with DNA respectively. There was no evidence for preferential removal of any of the four adducts (B, C, D, and I) during the 48 hr after treatment with benzo(a)pyrene. The relative resistance of rat skin, compared with mouse skin, to benzo(a)pyrene-induced skin carcinogenesis may be due in part to a lower extent of binding of benzo(a)pyrene to DNA, and a smaller percentage of both methanol-soluble hydrocarbon-deoxyribonucleoside adducts and of adducts derived from the putative ultimate carcinogen, BPDE. (Author abstract) (36 Refs)

36. OPTICALLY DETECTED MAGNETIC RESONANCE EVIDENCE FOR CARCINOGEN-NUCLEIC ACID INTERACTION IN THE TETRAHYDRO-9,10-EPOXYBENZO[E]PYRENE-DNA ADDUCT.

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J Am Chem Soc; 103(17):5257-5259 1981

The carcinogenic action of polycyclic aromatic hydrocarbons evidently is mediated by metabolically-activated intermediates which bind covalently to DNA. The optically-detected magnetic resonance technique was used to study the structure of the adduct of tetrahydro-9,10-epoxybenzo[e]pyrene (BePE) with DNA. The pyrene triplet chromophore in the BePE-DNA adduct appears to exist in an environment intermediate between complete intercalation and complete solvent exposure. (21 Refs)

37. CARCINOGEN-DNA ADDUCTS IN MUTAGENESIS ASSAYS.

Bigger CA, Dipple A, Tomaszewski JE, Lake RS
Chemical Carcinogenesis Program, Frederick Cancer Res. Center, Frederick, MD, 21701
Science; 213(4514):1411-1412 1981

Comparative studies of carcinogen metabolism in different systems to examine the assumption that the subcellular Aroclor-induced rat liver metabolizing system, recommended for general mutagenesis screening, effectively duplicated the activation of carcinogens in target tissue in vivo are described. In a series of studies, it was demonstrated that DNA-reactive metabolites of 7,12-dimethylbenz(a)anthracene generated by Aroclor-induced rat liver microsomes or S9 fraction differ substantially from those generated in intact cellular systems in vitro and a target tissue, mouse skin, in vivo. Studies with aflatoxin B1 and benzo(a)pyrene show no DNA adduct data for the Arochlor-induced rat liver system. It was suggested that the specific DNA adducts responsible for carcinogenesis are not known with certainty for any carcinogen, but that there is evidence to show that specific DNA reactive metabolites play a central role in carcinogenesis. Because of the wide application of these liver homogenates as models of in vivo activation in in vitro systems for the detection of potential carcinogens whose structure, pathways of metabolism, and mechanism of action are unknown, it was suggested that the accurate reproduction of in vivo activation cannot be assumed. (9 Refs)

38. DIFFERENCES IN THE BINDING OF 3-METHYLCHOLANTHRENE AND PHENOBARBITAL TO RAT LIVER CYTOSOLIC AND NUCLEAR PROTEIN FRACTIONS.

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Arch Biochem Biophys; 210(2):729-739 1981

In an effort to learn more about the induction of cytochromes P-450c and P-450b, two inducers of these cytochromes, 3-methylcholanthrene (3-MC) and phenobarbital (PB), respectively, were studied in their interactions with proteins from rat serum, rat liver cytosol, and rat liver nuclei. Using DNA-cellulose chromatography, it was demonstrated that 3-MC binds to both cytoplasmic and nuclear components (at approx 27 and 250-570 femtomole/mg of applied protein, respectively) and that PB does not bind to proteins from serum, cytosol, or nuclei that can bind to this chromatographic medium. No binding of PB to cytosolic proteins was demonstrated using DEAE A-50 Sephadex chromatography, charcoal dextran analysis, or sucrose density gradient centrifugation, but the binding of 3-MC to cytosolic proteins gave four peaks of radioactivity by the DEAE technique, two peaks by the sucrose gradient technique, and a specific binding of 0.13 picomole/mg protein by charcoal dextran analysis. One of the sucrose gradient peaks was labile in the presence of 0.3 M KCl, its disappearance being accompanied by an increase in the amplitude of the other peak. Following incubation with whole nuclei, the uptake and intranuclear distribution of 3-MC and PB differed markedly: 64% of the available 3-MC radioactivity but only 3% of the available PB radioactivity became associated with nuclei; moreover, the highest specific activity of this radioactivity was found in different locations, ie, associated with the 2 M KCl-resistant nuclear pellet for 3-MC and with the nuclear fraction soluble in the absence of salt for PB. Nuclear proteins that can bind to both polycyclic hydrocarbons and to DNA have not previously been reported. (43 Refs)

39. METABOLISM OF CHEMICAL CARCINOGENS BY CULTURED HUMAN AND RAT BLADDER EPITHELIAL CELLS.

Autrup H, Grafstrom RC, Christensen B, Kieler J
Lab. Environmental Carcinogenesis, Copenhagen, Denmark
Carcinogenesis; 2(8):763-768 1981

Cells from human bladder epithelium cell lines HU1689, HU1752, and HU1765 and primary bladder epithelial cells from Wistar rats were exposed in vitro for 24 hr to radioactively-labeled carcinogens dissolved in the medium: [1,3,6-3H]benzo[a]pyrene (BP) 1.5 uM; [G3H]aflatoxin B1 (AFB) 1.5 uM; [1 4C]N-nitrosodimethylamine (DMNA) 100 uM; [ethyl-1-14C]N-nitrosoethylmethylamine (EMNA) 100 uM; and [2,5-14C]N-nitrosopyrrolidine (NPy) 100 uM. The metabolism of the carcinogens was assayed by the release of metabolites into the culture medium and the binding of radioactive metabolites to DNA. The human bladder cells retained the capacity to metabolize chemical carcinogens. Binding of DNA occurred to a similar extent in all three cell lines. More BP was bound to DNA in human bladder cells than in rat bladder cells. More than 90% of the metabolites of BP in human cells consisted of organo-soluble products, primarily the 9,10-and 7,8-BP diols. N-nitrosamine metabolism produced CO2. NPy was oxidized in both the alpha and beta positions, predominantly alpha in human cells. EMNA was apparently metabolized, but did not bind to DNA. The results suggest that the human bladder may be able to activate carcinogens that come into direct contact with the epithelium, and that it utilizes pathways that are different from those found in other tissues and cells. (38 Refs)

40. DNA MODIFICATION IN RAT LUNGS FOLLOWING INTRATRACHEAL OR SUBCUTANEOUS ADMINISTRATION OF 4-NITROQUINOLINE-1-OXIDE, BENZO[A]PYRENE OR 2-AMINOANTHRACENE.

Harpaz R, Mitchell C
Inhalation Toxicology Res. Inst., Lovelace Biomedical and Environmental Res. Inst., P.O. Box 5890, Albuquerque, NM, 87115
Chem Biol Interact; 36(2):129-140 1981

Benzo[a]pyrene (BP)-,2-aminoanthracene (2AA)- and 4-nitroquinoline-1-oxide (4NQO)-mediated DNA modification were investigated in rat lungs by using alkaline sucrose gradient sedimentation. The exposure-route, the physicochemical nature of the administered compound and the number of treatments were all important in determining the extent of DNA modification. 4NQO produced qualitatively similar modification whether instilled intratracheally (it) as a suspension or injected sc in a soluble form. BP and 2AA produced no DNA alteration when injected sc; they did, however, modify DNA sedimentation when instilled as a suspension, but not until 24 hr after treatment. Furthermore, BP caused no DNA modification at any sampling time when instilled in a lipid solvent. In contrast to the DNA modification observed at 24 hr after a single it treatment with a BP suspension, no such alteration was detected 12 or 24 hr after the last of five similar daily treatments. These results are discussed with respect to mechanisms of differential transport, clearance and metabolism of administered carcinogens. (Author abstract) (36 Refs)

41. SPECIFIC LABELLING OF MICROSOMAL PROTEINS BY REACTIVE INTERMEDIATES GENERATED FROM 2-ACETYLAMINOFLUORENE IN VITRO.

Kaderbhai MA, Bradshaw TK, Freedman RB
Biological Lab., Univ. Kent, Canterbury, CT2 7NJ Kent, England
Chem Biol Interact; 36(2):211-227 1981

Incubation of 2-[9-14C]acetylaminofluorene (2-[9-14C]AAF) in vitro with rat live r microsomes, leads to covalent binding of label to microsomal proteins. The binding is NADPH-dependent, increases linearly with time, and is inhibited by SKF-525A and 7,8-benzoflavone (7,8-BF). Binding is increased more than eight-fold in microsomes from 3-methylcholanthrene (MC)-pretreated rats, but only less than two-fold in those from phenobarbital (PB)-pretreated rats. In the presence of cytosolic proteins, there is slight enhancement of the labeling of microsomes and some labeling of the cytosolic proteins. Sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE) and two-dimensional gel electrophoresis indicate that covalent labeling by 2-AAF derivatives is concentrated in specific proteins. The pattern of labelling varies between microsomes from animals pretreated with PB, MC and 2-AAF. Factors which may contribute to the specificity of labeling are discussed. (Author abstract) (21 Refs)

42. INDIRECT ALKYLATION OF CBA MOUSE LIVER DNA AND RNA BY HYDRAZINE IN VIVO. A POSSIBLE MECHANISM OF ACTION AS A CARCINOGEN.

Quintero-Ruiz A, Paz-Neri LL, Villa-Trevino S
(c/o Villa-Trevino) Departamento Investigacion, Division de Estudios, Superiores de la Facultad Medicina Universidad Autonoma de Chihuahua, Apart Postal 1506 Sucursal 'C' Chihuahua, Chihuahua, Mexico
JNCI; 67(3):613-618 1981

Treatment of inbred CBA mice with hydrazine sulfate, a liver carcinogen, plus [14C]formate or L-[methyl-14C]-methionine as a source of 'C1' units, produced [14C]7-methyl-guanine (7-MG) in liver DNA and RNA. This methylated guanine was identified by its chromatographic characteristics in three different systems: on Sephadex G10, on Dowex 50, and by paper co-chromatography with authentic 7-MG. Mice that received [14C]formate alone showed no 7-MG in their DNA or RNA. In addition, mice treated with L-[methyl-14C]methionine alone showed no 7-MG in their DNA. These results suggest that 'indirect' alkylation of nucleic acids is a mechanism of cancer initiation by hydrazine. (Author abstract) (20 Refs)

43. ON THE PECULIARITIES OF METHYLATION OF DNA OF DIFFERENT TISSUES OF RAT'S FETUS AND MATERNAL ORGANISM AFTER 1,2-DIMETHYLHYDRAZINE TREATMENT.

Likhachev AYa, Petrov AS
N. N. Petrov Res. Inst. Oncology, USSR Ministry Public Health, Leningrad, USSR
Vopr Onkol; 27(7):71-73 1981

A high rate of DNA methylation in the liver and large colon mucosa was registered 6 hr after dimethylhydrazine (SDMH) treatment of rats with 19-day gestations. However, in fetal liver, a low concentration of methylated guanine (7-methyl guanine) derivatives was found, while in large colon and brain, these substances were not detected at all. It is suggested that the resistance of embryonal tissues to the transplacental effect of SDMH is due to the underdeveloped enzymatic system of the fetus. (Author abstract) (8 Refs) (In RUS)

ALTERATION OF MIXED FUNCTION OXIDASES BY CARCINOGENS

44. EPOXIDE HYDROLASE ACTIVITY IN THE MITOCHONDRIAL AND SUBMITOCHONDRIAL FRACTIONS OF MOUSE LIVER.

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Dept. Entomology, Univ. California, Davis, CA, 95616
Biochem Pharmacol; 30(15):2111-2120 1981

Distribution of epoxide hydrolase activity in subcellular fractions of livers from male Swiss-Webster mice and Sprague-Dawley rats was monitored with trans-beta-ethylstyrene oxide, trans-stilbene oxide and benzo[a]pyrene 4,5-oxide following differential centrifugation. With the former two substrates the highest activity was encountered in the cytosolic fraction; however, significant activity was found in the mitochondrial fraction. These fractions hydrated benzo[a]pyrene 4,5-oxide very slowly, and the major benzo[a]pyrene 4,5-oxide hydrolyzing activity was recovered in the microsomal fraction. Using Triton WR-1339-treated mice, it was shown that trans-beta-ethylstyrene oxide hydrolyzing activity was predominantly localized in the mitochondria rather than in lysosomes and peroxisomes. Subsequent separation of the mitochondrial fraction into submitochondrial components by swelling, shrinking, and sonication, followed by sucrose density gradient centrifugation, showed that most of the epoxide hydrolyzing activity was present in the matrix and intermembrane space fraction. Significant activity was also present in the outer and inner membrane fractions. However, epoxide hydrolyzing activity in these fractions was reduced if either increased sonication times were used or the fractions were washed, indicating possible contamination of these fractions by the matrix and intermembrane space enzyme(s). The epoxide hydrolase activity in the mitochondrial and cytosolic fractions in mice appeared similar with regard to inhibition, mol wt, and substrate selectivity. (Author abstract) (44 Refs)

45. THE EFFECT OF 3-METHYLCHOLANTHRENE ON URINARY 6BETA-HYDROXYCORTISOL EXCRETION AND HEPATIC ENZYME ACTIVITY IN THE MARMOSET MONKEY (CALLITHRIX JACCHUS).

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Biochem Pharmacol; 30(15):2131-2134 1981

The effect of 3-methylcholanthrene treatment on the urinary excretion of 6beta-hydroxycortisol and hepatic enzyme activity was investigated in the marmoset monkey (Callithrix jacchus). 3-Methylcholanthrene increased cytochrome P-448 content, NADPH cytochrome-c reductase activity, 7-ethoxycoumarin O-deethylase activity and ethoxyresorufin O-deethylase activity but did not affect aminopyrine N-demethylase activity. This induction profile is qualitatively similar to that previously reported for the rat. There was no change in the ratio of urinary 6beta-hydroxycortisol to 17-hydroxycorticosteroids. The pattern of response to 3-methylcholanthrene indicates that cortisol 6beta-hydroxylase activity is not associated with induction of hepatic cytochrome P-488. (Author abstract) (8 Refs)

46. POLYHALOGENATED BIPHENYLS AND PHENOBARBITAL: EVALUATION AS INDUCERS OF DRUG METABOLIZING ENZYMES IN THE SHEEPSHEAD, ARCHOSARGUS PROBATOCEPHALUS.

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Chem Biol Interact; 36(2):229-248 1981

Several doses of Aroclor 1254 (polychlorinated biphenyl (PCB) mixture), Firemaster FFl (polybrominated biphenyl (PBB) mixture), 2,2',4,4',5,5'-hexabromobiphenyl (HBB), 3,3',4,4',5,5'-hexachlorobiphenyl (HCB) and phenobarbital (PB) were administered to the marine fish sheepshead (Archosargus probatocephalus). The PCB and PBB mixtures caused induction of hepatic microsomal benzo[a]pyrene hydroxylase (AHH), 7-ethoxycoumarin O-deethylase (7-EC) and 7-ethoxyresorufin O-deethylase (ERF) activities, but not benzphetamine N-demethylase (BND), epoxide hydrolase (EH) or glutathione S-transferase (GSH-T) activities. This induction pattern is typical of that caused by polycyclic aromatic hydrocarbons (PAH) in fish and mammals or by tetrachlorodibenzo-p-dioxin (TCDD) in mammals. The extent of induction of AHH-activity and cytochrome P-450 content was higher when experiments were carried out in summer (water temperature 25 +-4 C) than in winter (water temperature 11 +-3 C). Firemaster FFl (15 mg/kg) induced fish for at least 56 days in both summer and winter at which time the liver concentrations of PBB were in the ppm range. PCB concentrations in the ppm range have been found in fish from polluted lakes and seas, thus we may expect that environmental exposure to PCB is sufficient to induce hepatic mixed function oxidase (MFO) activities. The PCB isomer 3,3',4,4',5,5'-HCB, which induces the same spectrum of hepatic drug-metabolizing activities as TCDD and PAH in rats, had a broadly similar effect in the sheepshead. Another purified isomer 2,2',4,4',5,5'-HBB, which induces the same enzymes as PB in rats, had no effect on drug-metabolizing activities in sheepshead. PB was also without effect on sheepshead hepatic drug-metabolizing enzymes, although a typical narcotic effect was produced in PB-treated sheepshead. Our studies provide further evidence that drug-metabolizing activities in fish liver are readily induced by chemicals like TCDD or PAH, but we fail to demonstrate induction after treatment of sheepshead with inducers of the PB type. (Author abstract) (48 Refs)

47. EVIDENCE THAT BENZO(A)PYRENE-RESISTANT, ARYL HYDROCARBON HYDROXYLASE-DEFICIENT VARIANTS OF MOUSE HEPATOMA LINE, HEPA-1, ARE MUTATIONAL IN ORIGIN.

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Somatic Cell Genet; 7(4):373-388 1981

The ability of treatment with known mutagens to increase the frequency of benzo(a)pyrene resistant (BPr) variants was examined. The phenotypic stability of the variants was studied as a function of time in culture and with respect to the degree of heterogeneity among subclones. The in vitro heat lability of the aryl hydrocarbon hydroxylase (AHH) was examined. All strains used were derivatives of the subclone Hepa-1c1c7 of the mouse hepatoma line Hepa-1. Four agents with three distinctly different modes of mutagenic action were used: N-methyl-N'-nitro-N-nitrosoguanidine and ethyl methanesulfonate (alkylating agents), ICR-191G (frame-shift mutagen), and UV light were used. Except for one experiment in which ethyl methanesulfonate only gave a marginal response, the mutagens consistently increased the frequency of BPr clones in a dose-dependent manner. A positive correlation was observed between the frequencies of thioguanine-resistant and BPr clones produced. Many BPr clones possessed considerably reduced, or undetectable AHH activities. Even in those variants that retained considerable AHH activity, heterogeneity in AHH activity among cells of the variants was relatively slight. The sensitivity of BPr variants to the mutagen used for their isolation is described. The in vitro temperature lability of AHH activity in certain BPr variants is discussed. (8 Refs)

48. ALTERATIONS IN DRUG-METABOLIZING ENZYMES DURING FEEDING OF THE CARCINOGEN 2-AMINOANTHRAQUINONE.

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Toxicol Appl Pharmacol; 60(2):204-212 1981

Changes in enzymes which metabolize drugs during periods of feeding with 2-aminoanthraquinone (AAQ), at carcinogenic levels, were studied in young female Fischer 344 rats. Rats were fed 2% AAQ for 2, 4, 8 or 14 wk; after treatment, some were returned to the control diet. Some rats on the control diet were pair-fed with the AAQ group. At least four rats were available for each enzyme determination. Controls were fed ad libitum. Feeding AAQ increased liver content of cytochrome P-450, cytochrome b5, and increased NADPH-cytochrome c reductase activity as early as 2 wk. After 4 wk of AAQ, there was no change in azodye reductase, although an increase was observed in pair-fed controls. However, after 8 and 14 wk of AAQ, there was a significant increase in dimethylaminoazobenzene reductase. AAQ feeding also led to increased activities of benzo(a)pyrene hydroxylase, epoxide hydrolase, and alpha-naphthol-O-glucuronyl transferase. AAQ feeding beyond 4 wk increased the activities of N-demethylases, aniline hydroxylase and azo reductase. After the experimental period of AAQ feeding, the measured enzyme activities during the recovery period remained elevated in rats fed AAQ for 14 wk for 1 or 2 wk, and 2-4 wk in rats fed AAQ for 8 wk. (22 Refs)

ALTERATION OF OTHER CARCINOGEN-METABOLIZING ENZYMES BY CARCINOGENS

49. EFFECT OF BENZO(A)PYRENE AND ITS NONCARCINOGENIC ANALOG 1,2-BENZOPYRENE ON NA,K-ATPASE ACTIVITY OF HOMOGENATES OF VARIOUS MOUSE ORGANS AND OF MEMBRANE PREPARATION FROM RAT HEART.

Mustafin AM, Kim SCh
Kazakh Inst. Oncology and Radiology, Alma-Ata, USSR
Biull Eksp Biol Med; 91(7):76-77 1981

The effect of benzo(a)pyrene (BP) and its noncarcinogenic analog 1,2-benzopyrene (1,2-BP) on Na, K-ATPase activity was studied in homogenates of albino mice lungs, stomach, and liver. BP caused significant inhibition of enzyme activity in the lungs and in the stomach; the inhibitory effect of 1,2-BP was less pronounced. Both BP and 1,2-BP did not inhibit the enzyme activity of liver homogenate and activity of Na ,K-ATPase from the membranes of rat heart. (5 Refs) (In RUS)

50. ENZYME DEVIATION PATTERNS IN PRIMARY RAT HEPATOMAS INDUCED BY SEQUENTIAL ADMINISTRATION OF TWO CHEMICALLY DIFFERENT CARCINOGENS.

Sato K, Hatayama I, Hoshino K, Imai F, Tsuchida S, Sato T, Nishimura K, Tatematsu M, Ito N
Second Dept. Biochemistry, Hirosaki Univ. Sch. Medicine, Hirosaki 036, Japan
Cancer Res; 41(10):4147-4153 1981

Enzyme deviation patterns were examined in primary rat hepatomas induced by short-term sequential administration of two chemical carcinogens from among 2-fluorenylacetamide (FAA), diethylnitrosamine (DENA), and 3'-methyl-4-dimethylaminoazobenzene (3'-Me-DAB) or by FAA or 3'-Me-DAB followed by phenobarbital as a promoter. The purpose was to discern how the patterns are influenced by different administration schedules of carcinogens and which of the two carcinogens in the sequence affects the patterns more. Biochemical differentiation of hyperplastic hepatic nodules and hepatomas was determined by simultaneous assays of activities and isozyme composition of glucose-adenosine triphosphate phosphotransferase, pyruvate kinase, glucose-6-phosphatase, fructose-1,6-biphosphatase, and gamma-glutamyltransferase with consideratio of histological classification of nodules and tumors. Poorly differentiated hepatomas were predominantly induced by 3'-Me-DAB followed by FAA or DENA except for hepatomas induced by 3'-Me-DAB followed by phenobarbital, which were mainly well and moderately differentiated; well and moderately differentiated hepatomas were predominantly induced by FAA followed by 3'-Me-DAB or phenobarbital. The degree of enzyme deviation of the hepatomas induced by DENA as the first carcinogen was intermediate between those of hepatomas induced by FAA or 3'-Me-DAB, although the degree tended to increase with increased dose or term of DENA. These results indicate that deviations of some enzymes, such as pyruvate kinase and fructose-1,6-bisphosphatase, as well as histological differentiation of the primary hepatomas are more strongly influenced by the first carcinogen than by the second under our administration schedules and that the degree of enzyme deviation shown by hepatomas produced by a particular carcinogen treatment regimen principally relates to the potential of that regimen to induce the more anaplastic tumors. (Author abstract) (33 Refs)

51. HEPATOCELLULAR CARCINOMA INDUCED BY ESTROGEN AND PROGESTOGEN: DEVELOPMENT OF HEPATOCELLULAR CARCINOMA IN RATS FOLLOWING ORAL ADMINISTRATION OF SYNTHETIC ESTROGEN AND PROGESTOGEN.

Higashi S
First Dept. Surgery, Mie Univ. Sch. Medicine, Tsu, Japan
Mie Med J; 30(3):295-303 1981

Female Wistar rats were given daily 0.075 mg of ethinyl-estradiol (EES) and 6 mg of norethindrone acetate (NEA) dissolved in olive oil by gavage for 1 yr, another group received similar treatment for 18 mo, and a third group received olive oil alone for 1 yr and served as controls for the first group. In rats treated with EES and NEA, the liver wt increased markedly, while the body wt decreased. In the rats treated for 18 mo, the activities of glutamine oxaloacetic transaminase, glutamic pyruvic transaminase, and lactic dehydrogenase were higher and total cholesterol and triglyceride were lower, than those treated for only 1 yr. Multiple nodules ranging from 0.2 mm to 1 mm in diameter were observed in all the treated rats. These were hyperplastic nodules with compression and atrophy of the surrounding liver parenchyma. One of the 18 rats in the first group had a large, 2.5 x 2.0 x 1.5 cm, well-differentiated hepatocellular carcinoma composed of trabeculae of neoplastic cells. In rats treated for 18 mo, the number of hyperplastic nodules was higher and their size was larger than animals treated for 12 mo. These results support the hypothesis that EES and NEA may be initiators in hepatocarcinogenesis. (30 Refs)

REVIEWS AND OTHER RELEVANT STUDIES

52. EXPERIMENTAL APPROACHES TOWARDS THE BIOCHEMICAL ANALYSIS OF CHEMICAL CARCINOGENESIS.

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ACS Symp Ser; 160:197-215 1981

Developments in chemical carcinogenesis research as they affect the understanding of malignancy at the molecular level are reviewed. Early observations noted the relationship between exposure of humans to certain substances and the occurrence of certain cancers. This led to laboratory experiments demonstrating the induction of cancers in animals by purified chemicals. Carcinogenesis was further depicted as a two-stage process. The first step involved initiation of cancer potential in cells by a carcinogen. The second step involved promotion of cancer development by a promoting substance that might be different from the initiator. The importance of the presence of various antagonistic carcinogens, enzymes, and metabolites of carcinogens was recognized as affecting the development of cancer or the lack of it. Molecular analysis showed that carcinogens are electrophilic molecules that bind to the DNA molecules in target cells. Current research is exploring the importance of cell cycle phase on carcinogenesis. Cell lineage and genotypic cell markers are being studied as tools for cancer research. (91 Refs)

53. APPLICATION OF A GEOMETRIC PARAMETER DEFINING MOLECULAR SHAPE, FOR THE QUANTITATION OF INTERACTION OF POLYCYCLIC AROMATIC HYDROCARBONS WITH ENZYME SYSTEMS.

Lamparczyk H, Radecki A, Kaliszan R

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Biochem Pharmacol; 30(16):2337-2341 1981

Quantitative relationships between the ability of polycyclic aromatic hydrocarbons to induce and repress various enzyme systems and a geometric parameter expressing their molecular shape have been described. In contrast, no statistically significant relationship was found when quantum-chemical parameters characterizing the reactivity and donor-acceptor properties of these compounds were correlated with their biological activity. (Author abstract) (17 Refs)

54. ENDOGENOUS CARCINOGENS.

Hill MJ

Bacterial Metabolism Res. Lab., Central Public Health Lab., London, England

Practitioner; 225(1356):803-804,807-809 1981

Estradiol is a potential endogenous carcinogen. Consuming a high fat/high energy diet, by increasing circulating estrogen levels and estrogen receptor activity, may increase the risk of carcinogenesis in estrogen-dependent tissues (breast, endometrium, possibly ovary). The role of of cholesterol in carcinogenesis is not yet clear. The author's studies showed no relationship between fecal cholesterol levels and the risk of intestinal cancer in case-control studies. Some of the numerous urinary metabolites of tryptophan seem to be related to non-industrial bladder cancer. Intestinal bacteria can derive carcinogenic substances (ethionine, phenol, p-cresol, N-nitroso compounds, bile acid metabolites, etc) from dietary components and convert exogenous chemicals (eg, polycyclic aromatic hydrocarbons) to proximate carcinogens. It is relatively easy to determine which carcinogens might be produced under ideal conditions, but there is limited information on which carcinogens are actually produced in vivo, and very little information regarding their importance. (27 Refs)

55. UPTAKE OF LIPOPHILIC CARCINOGENS BY PLASMA LIPOPROTEINS. STRUCTURE-ACTIVITY STUDIES.

Shu HP, Nichols AV
Lawrence Berkeley Lab., Univ. California, Berkeley, CA, 94720
Biochim Biophys Acta; 665(3):376-384 1981

This report describes the interaction between plasma lipoproteins and two hydroxylated metabolites of benzo[a]pyrene, 3-hydroxybenzo[a]pyrene and benzo[a]pyrene-7,8-dihydrodiol, whic h differ significantly in lipophilicity. When incubated with plasma, the metabolites of benzo[a]pyrene exhibit a decreasing distribution into the ultracentrifugal lipoprotein fraction (d less than or equal to 1.20) and an increasing distribution into the albumin-rich fraction (d greater than 1.20) as the degree of hydroxylation of the metabolite increases. At saturation, uptake of benzo[a]pyrene by VLDL, LDL and HDL correlates with lipoprotein total-lipid vol. Uptake of hydroxylated derivatives per lipoprotein total-lipid vol, in general, decreases with increasing hydroxylation. Contrary to this trend, HDL uptake of 3-hydroxybenzo[a]pyrene at saturation is significantly higher than its uptake of benzo[a]pyrene. Uptake of benzo[a]pyrene-7,8-dihydrodiol per total-lipid vol by all of the lipoprotein classes at saturation is considerably lower than their uptake of 3-hydroxybenzo[a]pyrene. Factors in addition to lipid solubility substantially alter lipoprotein uptake of the metabolites. (Author abstract) (15 Refs)

56. CYTOTOXIC AND CLASTOGENIC EFFECTS OF SOLUBLE AND INSOLUBLE COMPOUNDS CONTAINING HEXAVALENT AND TRIVALENT CHROMIUM.

Levis AG, Majone F
Inst. Animal Biology, Univ. Padua, Padua, Italy
Br J Cancer; 44(2):219-235 1981

Cr(III) and Cr(VI) compounds of varying solubilities have been tested in vitro for their ability to inhibit cell growth and nucleic acid and protein syntheses in BHK cells, to induce alterations in the mitotic cycle in HEp cells, and to increase the frequency of chromosomal aberrations and sister chromatid exchanges (SCE) in CHO cells. All Cr(VI) compounds, and particularly those containing soluble Cr(VI), such as potassium dichromate and zinc yellow, differentially inhibit macromolecular syntheses in BHK cells, that of DNA being always the most affected. Among Cr(III) compounds, which generally have very low cytotoxicity, chromite is particularly active, and inhibits cell growth and DNA synthesis even more than the poorly soluble Cr(VI) compounds. Preincubation in growth medium, with or without metabolizing cell cultures, solubilizes considerable amounts of Cr(VI) from zinc yellow and chromite, but significant amounts are also obtained from the most insoluble Cr(VI) pigments. When BHK cells are treated with such preincubated solns, reduction of soluble Cr(VI) to Cr(III) by cell metabolites is seen with all Cr(VI) compounds, accompanied by decreased cytotoxicity. The same differences between Cr(VI) and Cr(III) compounds apply to the cytotoxic effects on mitosis of HEp cells and the clastogenic effects on CHO cells. The activity of chromite, the only Cr(III) pigment capable of significantly increasing the frequency of SCE, is due to contamination with soluble Cr(VI). In contrast to the very low cytotoxicity of Cr(III), much higher chromium levels are detected in the cells incubated with soluble Cr(III) than with the same concentrations of soluble Cr(VI). 50% and 75% of chromium accumulated in the cells during treatments with Cr(VI) and Cr(III) respectively remains firmly bound to the cells, even when they are incubated for up to 48 hr in normal growth medium. Chromium accumulated in the cells after treatment with Cr(III) is most probably bound to the cell membrane, whereas some of the Cr(VI) is transported through the cell membrane and reduced in the cell nucleus. The results of the present investigation are in agreement with those obtained with the same Cr(VI) and Cr(III) compounds in mutagenicity assays in bacteria and carcinogenicity tests in rodents. A re-evaluation of the mechanisms of chromium carcinogenesis is proposed. (Author abstract) (54 Refs)

57. THE ROLE OF GENETIC TOXICOLOGY IN A SCHEME OF SYSTEMATIC CARCINOGEN TESTING.

Williams GM, Weisburger JH, Brusick D
Naylor Dana Inst. for Disease Prevention, American Health Foundation, Valhalla, NY, 10595
ACS Symp Ser; 160:57-87 1981

No single test has been developed for detecting all hazardous chemicals. It is therefore important to formulate the criteria for selecting the best combination of tests for a test battery. A battery should combine detection and confirmation of a hazard in one step. It should be capable of including all types of hazards. The tests should have clear biological significance and should maximize metabolic parameters. The Decision Point Approach involves five sequential steps in evaluating the carcinogenic potential of a chemical. First the structure of the chemical is determined. Then a series of in vitro short-term tests are run. These tests include bacterial mutagenesis, DNA repair, mammalian mutagenesis, sister chromatid exchange, and cell transformation. The evidence provided by the tests is evaluated. A suspected chemical is tested in limited in vivo assays for skin tumor induction in mice, pulmonary tumor induction in mice, breast cancer induction in female Sprague-Dawley rats, and altered foci induction in rodent liver. Further evaluation is made. Chronic bioassays complete the series of tests. A final evaluation of all the tests is made, allowing a decision to be made on the hazard of the chemical in question. (63 Refs)

58. PANCREATIC CANCER.

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UICC Tech Rep Ser. Vol. 57, Issue 12, 142 pp., 1981.

The objectives of the International Union Against Cancer Workshop were to bring together a small group of active workers in the basic aspects of pancreatic cancer (PC) with the hope that by their carefully planned interchange, they might summarize current information and provide some guidelines for future research. Topics discussed included the epidemiology of PC (international incidence data, time trends, urban/rural differences, socioeconomic differences, and risk factors), pathology of PC (nonendocrine: types of PC), cell structure and function of endocrine PC (synopsis of current views on pancreatic islet cytology, analysis of cell structure and secretory products in endocrine PCs, experimental tumors, mixed endocrine-exocrine PC, and perspectives for future work), carcinogenesis (pancreatic carcinogenesis, carcinogen metabolism, and histogenesis of PC), animal models, biology of pancreatic tumor cells, tumor markers (carcinoembryonic antigen (CEA), pancreatic oncofetal antigens (POA), comparison of POA and CEA, search for other new PC markers, comparison of CEA and anti-CEA reactive substances in colonic and pancreatic tumors, identification and evaluation of protein degradation products resulting from protease activities associated with PC, leukocyte adherence inhibition, galactosyl transferase isoenzyme in PC, and radioimmunodetection), effects of diet on the exocrine pancreas, aims and decision in PC with regard to the relationship between tumor and host (current methods of treatment, prognostic factors, and therapeutic strategy), and conclusions and recommendations for future work. (432 Refs)

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NOTICE OF CURRENT REVIEWS: CARCINOGENESIS

As an additional service to readers of carcinogenesis (CK series) CANCERGRAMS, each issue now provides a bibliography of review articles of interest to carcinogenesis researchers, selected from journals screened for that month's CANCERGRAMS.

CHEMICAL CARCINOGENESIS

1. TOXICOLOGICAL ASPECTS OF POLYCYCLIC AROMATIC HYDROCARBONS (PAH).

De Fernicola NA, De Azevedo FA
Divisao de Toxicologia e Ecotoxicologia, Diretoria de Tecnologia e Desenvolvimento, Sao Paulo, Brazil
Rev Bras Saude Ocup; 33(9):62-68 1981
In POR

2. EVALUATION OF THE CARCINOGENIC RISK OF CHEMICALS TO HUMANS: SOME ANTINEOPLASTIC AND IMMUNOSUPPRESSIVE AGENTS.

International Agency for Research on Cancer
International Agency for Res. on Cancer, Lyon, France
IARC Monogr Eval Carcinog Risk Chem Hum; 26:1-411 1981

3. STUDIES ON THE ROLE OF ORAL CONTRACEPTIVE USE IN THE ETIOLOGY OF BENIGN AND MALIGNANT LIVER TUMORS.

Mettlin C, Natarajan N
Cancer Control and Epidemiology, Rosewell Park Memorial Inst., 666 Elm St., Buffalo, NY, 14263
J Surg Oncol; 18(1):73-85 1981

RADIATION CARCINOGENESIS

4. EXPERIMENTAL RADIATION CARCINOGENESIS: WHAT HAVE WE LEARNED?

Fry RJ
Biology Div., Oak Ridge Natl. Lab., Oak Ridge, TN, 37830
Radiat Res; 87(2):224-239 1981

5. INFLUENCE OF NONCARCINOGENIC SECONDARY FACTORS ON RADIATION CARCINOGENESIS.

Little JB
Lab. Radiobiology, Harvard Univ., Sch. Public Health, Boston, MA, 02115
Radiat Res; 87(2):240-250 1981

6. MEDICAL IRRADIATION IN JAPAN - STOCHASTIC RISK ESTIMATION AND ITS REDUCTION.

Hashizume T
Div. Physics, National Inst. Radiological Sciences, 9-1 Anagawa 4-Chome, Chiba Shi 260, Japan
Nippon Igaku Hoshasen Gakkai Zasshi; 41(5):445-474 1981
In JPN

7. RADIOACTIVITY IN DRINKING WATER.

Cothern CR
Office of Drinking Water, Environmental Protection Agency, Washington, DC
Radioactivity in Drinking Water. Available from National Technical Information Service, Springfield, VA, as PB81-192833:, 79 pp., 1981.

EPIDEMIOLOGY, ETIOLOGY AND GENETIC ASPECTS OF HUMAN CANCER

8. EPIDEMIOLOGY OF GASTROINTESTINAL CANCER.

Miller AB
NCIC Epidemiology Unit, Univ. Toronto, McMurrich Building, Toronto, Ontario M5S 1A8, Canada
Compr Ther; 7(8):53-58 1981

9. EPIDEMIOLOGICAL ASPECTS OF ESOPHAGEAL CANCER.

Ruggieri M, Tosato F, De Rocco K, Lepore M, Cipriano E, Paolini A
IV Cattedra di Clinica Chirurgica Generale e Terapia Chirurgica, Universita degli Studi di Roma, Rome, Italy
Recenti Prog Med; 70(5):545-556 1981
In ITA

10. PANCREATIC CANCER.

Cohn I, Hastings PR
.Dept. Surgery, Louisiana State Univ., 1542 Tulane Ave., New Orleans, LA, 70112
UICC Tech Rep Ser. Vol. 57, Issue 12, 142 pp., 1981.

11. GENETICALLY DETERMINED SUSCEPTIBILITY TO CANCER.

Marks PA
Memorial Sloan-Kettering Cancer Center, 1275 York Ave., New York, NY, 10021
Blood; 58(3):415-419 1981

12. ETIOLOGY, ROLE AND DETECTION OF CHROMOSOMAL ABERRATIONS IN MAN.

Fabricant JD, Legator MS
Dept. Preventive Medicine, Div. Environmental Toxicology, Univ. Texas Medical Branch, Galveston, TX, 77550
JOM; 23(9):617-625 1981

ENVIRONMENTAL AND OCCUPATIONAL FACTORS IN CARCINOGENESIS

13. INDUSTRIAL CARCINOGENESIS.

Vickers CF
Dept. Dermatology, Univ. Liverpool, Liverpool L69 3BX, England
Br J Dermatol; 105(Suppl21):57-61 1981

14. ENVIRONMENT AND HEALTH (LITERATURE REVIEW).

Khachatrian TS
Dept. Public Health, State Inst. Advanced Training for Physicians, Erevan, USSR
Zh Eksp Klin Med; 21(3):287-292 1981
In RUS

15. LIFESTYLE AND CANCER.

Higginson J
International Agency for Res. on Cancer, Lyon, France
Cancer Forum; 5(1):4-14 1981

16. ASBESTOS. AN ENVIRONMENTAL POLLUTANT.

Zamfir G, Diaconu R
Institutul de igiena si sanatate publica, Iasi, Romania
Igiena; 30(1):1-9 1981
In RUM

17. REVIEW OF UICC PROGRAM ON SMOKING AND LUNG CANCER.

Gray N
Smoking and Cancer Program, UICC, 3 rue du Conseil General, 1205 Geneva, Switzerland
Cancer Forum; 5(1):15-18 1981

CELLULAR AND MOLECULAR MECHANISMS IN CARCINOGENESIS

18. EXPERIMENTAL APPROACHES TOWARDS THE BIOCHEMICAL ANALYSIS OF CHEMICAL CARCINOGENESIS.

Laishes BA
McArdle Lab. for Cancer Res., Univ. Wisconsin Medical Sch., Madison, WI, 53706
ACS Symp Ser; 160:197-215 1981

19. FIBRONECTIN AND RELATED TRANSFORMATION-SENSITIVE CELL SURFACE PROTEINS (ONCOLOGY OVERVIEW).

International Cancer Research Data Bank
ICRDB Program Office, NCI, Westwood Building, Room 10A18, Bethesda, MD, 20205
Fibronectin and Related Transformation-Sensitive Cell Surface Proteins (Oncology Overview) Chen, L B, ed This Title is Available Through National Technical Information Service, Springfield, VA, as NTISUB/PB81-923001:; OB-81/01:95pp. 1981

20. PRENEOPLASTIC LESIONS OF THE MAMMARY GLAND. (ONCOLOGY OVERVIEW)

International Cancer Research Data Bank
ICRDB Program Office, NCI, Westwood Building, Room 10A18, Bethesda, MD, 20205
Preneoplastic Lesions of the Mammary Gland (Oncology Overview) Medina, D, ed This Title is Available Through National Technical Information Service, Springfield, VA, as NTISUB/PB81-923002; OB-81/02:134pp. 1981

21. LYMPHOCYTE DIFFERENTIATION: AN ESSENTIAL BASIS FOR THE COMPREHENSION OF LYMPHOID NEOPLASIA.

Magrath IT
Pediatric Oncology Branch, Div. Cancer Treatment, NCI, NIH, Public Health Service, United States Dept. Health and Human Services, Bethesda, MD, 20205
JNCI; 67(3):501-514 1981

MODIFICATION OF CARCINOGENESIS

22. FACTORS STIMULATING AND INHIBITING TUMOR GROWTH IN CARCINOGENESIS.

Kochergina NI, Kosova IP
Res. Lab. Experimental Immunobiology, Moscow, USSR
Usp Sovrem Biol; 91(3):409-418 1981
In RUS

23. TWO INDEPENDENT ASPECTS OF TUMOR PROMOTION.

Berenblum I, Armuth V
Weizmann Inst. Science, Rehovot, Israel
Biochim Biophys Acta; 651(1):51-63 1981

VIRAL AND IMMUNOLOGICAL ASPECTS OF CARCINOGENESIS

24. BURKITT'S LYMPHOMA.

Ziegler JL
NCI, Bethesda, MD, 20205
N Engl J Med; 305(13):735-745 1981

25. REVIEW ARTICLE. REGULATION OF EXPRESSION OF THE INTEGRATED RETROVIRUS GENOME.

Weinberg RA, Steffen DL
Center for Cancer Res., Massachusetts Inst. Technology, Cambridge, MA, 02139
J Gen Virol; 54(part1):1-8 1981

METHODOLOGY IN CARCINOGENESIS RESEARCH

26. THE DEVELOPMENT AND VALIDATION OF MUTAGENICITY SCREENING TESTS.

Durkin PR, Santodonato J
Center for Chemical Hazard Assessment, Syracuse Res. Corporation, Merill Lane, Syracuse, NY, 13210
Tappi; 64(9):153-159 1981

27. SHORT-TERM TEST SYSTEMS FOR POTENTIAL MUTAGENS AND CARCINOGENS: I. MICROBIAL TESTS (ONCOLOGY OVERVIEW).

International Cancer Research Data Bank
ICRDB Program Office, NCI, Westwood Building, Room 10A18, Bethesda, MD, 20205
Short-Term Test Systems for Potential Mutagens and Carcinogens: I Microbial Tests (Oncology Overview) Simmon, V F; Peirce, V; eds This Title is Available Through National Technical Information Service, Springfield, VA, as NTISUB/PB81-922903:; OK-81/03:124pp. 1981

28. ANIMAL MODELS OF INTRA-ORAL CHEMICAL CARCINOGENESIS: A REVIEW.

Eveson JW
Dept. Oral Medicine and Pathology, Guy's Hosp., London SE1 9RT, England
J Oral Pathol; 10(3):129-146 1981

29. THE CHROMOSOMES IN HEMATOLOGY.

Berger R
Laboratoire de Cytogenetique, Institut de Recherches sur les Leucemies et les Maladies du Sang, UER d'Hematologie, Hopital Sant-Louis, 2 place du Dr. Fournier, 75475 Paris Cedex 10, France
Cancer Genet Cytogenet; 4(1):69-88 1981

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ICRDB CANCERGRAM

MECHANISMS OF CARCINOGENESIS

Activation and Metabolism of Carcinogens

SERIES CK08 No. 82/02

FEBRUARY, 1982

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METABOLIC ACTIVATION OF CARCINOGENS

1. ACTIVATED METABOLITES OF CARCINOGENIC HYDROCARBONS.

Harvey RG
Ben May Lab., Univ. Chicago, Chicago, Il , 60637
Acc Chem Res; 14(7):218-226 1981

Elucidation of the structures of active polycyclic aromatic hydrocarbon metabolites and of the pathways leading to their formation are reviewed with respect to implications for the mechanism of cancer induction. Major topics discussed include

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metabolism, K-region arene oxides, diol epoxide metabolites of other polyarenes, diol epoxide-nucleic acid interaction, and theories of carcinogenesis. Although much is now known in the areas of metabolic activation and tumor initiation, unanswered questions remain concerning the relation of DNA alkylation and tumor induction, regioselectivity of alkylation, fidelity of transcription, and nucleic acid repair and errors during repair. (123 Refs)

2. ENZYMATIC METHYLATION OF MICROSOMAL METABOLITES OF BENZO(A)PYRENE.

Lombardi PE, Mayhew JW, Goldin BR, Gregory ME, Lynch MA, Sullivan CE, Gorbach SL
(c/o Mayhew) Infectious Disease Service, New England Medical Center Hosp., 171 Harrison Ave., Boston, MA, 02111
Cancer Res; 41(11,part1):4415-4419 1981

These studies suggest that the microsomal metabolism of benzo(a)pyrene (BP) produces metabolites which can be methylated by the catechol-o-methyltransferase (COMT)/S-adenosylmethionine (SAM) enzyme/donor combination. Induced microsomes converted 12 to 15% of substrate BP to polar products. Approx 0.06% of substrate BP was recovered as COMT/SAM-reactive substances. In tests for specificity, COMT/SAM was found to react with catechols, but not with dihydrodiols, quinones, a phenol, an epoxide, or 1,4-hydroquinone. Organic extracts of COMT/[14C]SAM incubations with BP were fractionated by high-performance liquid chromatography. The appearance of radiolabeled chromatographic bands required the presence of substrate BP, microsomes, and COMT/[14C]SAM. When the Ames mutagenesis assay was supplemented with COMT/SAM, a 36% reduction was observed in the number of revertant colonies induced by the microsomal oxidation of BP. In contrast, the mutagenic properties of 2-aminofluorene were not affected by COMT/SAM. These observations indicate that COMT/SAM does not generally inhibit mixed-function oxidase activity but rather reacts with substances which are activated by ring oxygenations. (Author abstract) (33 Refs)

3. REDUCTION OF TUMORIGENICITY AND OF DIHYDRODIOL FORMATION BY FLUORINE SUBSTITUTION IN THE ANGULAR RINGS OF DIBENZO(A,I)PYRENE.

Hecht SS, LaVoie EJ, Bedenko V, Pingaro L, Katayama S, Hoffman D, Sardella DJ, Boger E, Lehr RE
Naylor Dana Inst. Disease Prevention, American Health Foundation, Valhalla, NY, 10595
Cancer Res; 41(11,part1):4341-4345 1981

The tumor-initiating activities on mouse skin and in vitro metabolism of dibenzo(a,i)pyrene, 2-fluorodibenzo(a,i)pyrene, 3-fluorodibenzo(a,i)pyrene, and 2,10-difluorodibenzo(a,i)pyrene were compared. After an initiating dose of 500 ug, followed by promotion with tetradecanoylphorbol acetate, dibenzo(a,i)pyrene induced skin tumors in 85% of the mice and caused 5.8 skin tumors/mouse. The corresponding tumorigenic activities for the fluorinated compounds were: 2-fluorodibenzo(a,i)pyrene (85%; 1.7 tumors/mouse); 3-fluorodibenzo(a,i)pyrene (80%; 3.1 tumors/mouse); and 2,10-difluorodibenzo(a,i)pyrene (10%; 0.1 tumors/mouse). After an initiating dose of 100 ug, only dibenzo(a,i)pyrene showed significant tumor-initiating activity. 3,4-Dihydro-3,4-dihydroxydibenzo(a,i)pyrene was identified as a metabolite of dibenzo(a,i)pyrene formed by the 9000 x g supernatant from the livers of Aroclor 1254-pretreated rats. Another dihydrodiol was tentatively identified as 1,2-dihydro-1,2-dihydroxydibenzo(a,i)pyrene. The formation on these angular ring dihydrodiols was inhibited in the metabolism of 2-fluorodibenzo(a,i)pyrene and 3-fluorodibenzo(a,i)pyrene. Angular ring dihydrodiols were not detected in the metabolism of 2,10-difluorodibenzo(a,i)pyrene. These results suggest that an angular ring dihydrodiol, 3,4-dihydro-3,4-dihydroxydibenzo(a,i)pyrene, which can form a bay-region dihydrodiol epoxide, may be a proximate carcinogen of dibenzo(a,i)pyrene. (Author abstract) (25 Refs)

4. QUANTUM CHEMICAL STUDIES OF METHYL AND FLUORO ANALOGS OF CHRYSENE: METABOLIC ACTIVATION AND CORRELATION WITH CARCINOGENIC ACTIVITY.

Poulsen MT, Loew GH
(c/o Loew) Life Sciences Div., SRI International, 333 Ravenswood Ave., Menlo Park, CA, 94025
Cancer Biochem Biophys; 5(2):81-90 1981

Specific electronic properties related to metabolic transformation and adduct formation by DNA were calculated for a series of methyl, dimethyl and n-fluoro-5-methyl derivatives of chrysene with the aim of identifying molecular properties which could be used as reliable indicators of their relative carcinogenic behavior. Using the semiempirical all valence electron IEHT method, the bay region bonds of 5MC were found to have enhanced nucleophilic reactivity to epoxide formation relative to chrysene. In addition, in one of the nonequivalent bay regions, the 1, 2, 3, 4 region, the distal (1, 2) bond was found to be more reactive than the proximal (3, 4) bond. This reactivity pattern leads to an easily formed diol epoxide carbocation, the postulated ultimate carcinogen. By contrast, in the other (7, 8, 9, 10) bay region, the proximal (9, 10) bond is the more reactive, suggesting formation of the 'wrong,' ie, less stable diol epoxide carbocation. Consistent with earlier studies of other PAH, calculations by the INDO method of the ease of carbocation formation from a bay region diol epoxide yielded a set of values which gave a good correlation with carcinogenicity. (Author abstract) (29 Refs)

5. STUDIES IN THE METABOLISM OF CARCINOGENIC POLYCYCLIC HETEROAROMATIC COMPOUNDS. I. THE HEPATIC MICROSOMAL METABOLISM OF 7-METHYLBENZ[C]ACRIDINE.

Ireland CM, Holder GM, Ryan AJ
(c/o Holder) Dept. Pharmacy, Univ. Sydney, New South Wales 2006, Australia
Biochem Pharmacol; 30(19):2685-2690 1981

An enzyme assay for the metabolism of the carcinogenic aza-aromatic polycyclic compound 7-methylbenz[c]acridine has been developed using a modification of a radiochemical assay described for the polycyclic aromatic hydrocarbon benzo[a]pyrene by DePierre et al and Van Cantfort et al. When the activities of controlled microsomes and microsomes of phenobarbital-, 3-methylcholanthrene- and 7-methylbenz[c]acridine-pretreated animals were compared, strong similarities were displayed toward oxidation of benzo[a]pyrene and 7-methylbenz[c]acridine. These similarities were seen in turnover numbers, Michaelis constants, and inducibility of both enzyme systems. 7-Methylbenz[c]acridine afforded a Type I difference spectrum with 3-methylcholanthrene-pretreated microsomes. It is suggested that 7-methylbenz[c]acridine is oxidized by the same or a similar set of enzymes which is responsible for benzo[a]pyrene metabolism. (Author abstract) (39 Refs)

6. RELATIONSHIP OF METABOLIC ACTIVATION OF N-HYDROXY-N-ACYLARYLAMINES TO BIOLOGICAL RESPONSE IN THE LIVER AND MAMMARY GLAND OF THE FEMALE CD RAT.

Shirai T, Fysh JM, Lee M, Vaught JB, King CM
(c/o King) Dept. Chemical Carcinogenesis, Michigan Cancer Foundation, Detroit, MI, 48201
Cancer Res; 41(11,part1):4346-4353 1981

Ip injection of the N-formyl, N-acetyl, or N-propionyl derivatives of N-hydroxy-4-aminobiphenyl, N-hydroxy-2-acetylaminofluorene, or N-(4-biphenyl)glycolamide disclosed that the ability of these compounds to induce mammary tumors in the female CD rat was greater if the compound was able to be metabolized to a reactive product by one of two soluble enzymes obtained from both the liver and mammary gland. A similar but weaker association between the formation of gamma-glutamyltranspeptidase-positive foci and cellular altered foci of the liver was also observed. The enzyme related to the tumorigenicity of these compounds was characterized by a highly specific capacity to form adducts from the acetyl and propionyl derivatives. The other enzyme exhibited greater activity with N-formyl substrates. The two enzyme activities were separable by ion-exchange chromatography on DEAE-cellulose and by gel filtration of Sephacryl. Liver microsomes also possessed the capacity to activate both the formyl and acetyl derivatives to reactive species; formyl substrates were 7 to 8x more active than acetylated compounds. The microsomal activities and the formyl-preferring soluble enzyme were inhibited by diethyl-p-nitrophenylphosphate, a microsomal deacylase inhibitor. The cytosolic enzymes that are most active with the acetyl and propionyl substrates were little affected by this organophosphate compound. The microsomal activation was not due solely to deacylation of the hydroxamic acids, since formylated and acetylated substrates were hydrolyzed at approx the same rates. (Author abstract) (37 Refs)

OTHER METABOLISM OF CARCINOGENS

7. DIFFERENCES IN ROUTES OF CONJUGATION WITH GLUCURONIC ACID AND SULPHATE IN NORMAL AND CANCEROUS TISSUE FROM HUMAN LUNG.

Mehta R, Gibby EM, Cohen GM
Div. Toxicology, Dept. Biochemistry, Univ. Surrey, Guildford GU2 5XH, Surrey, England
Biochem Soc Trans; 9(1):110-111 1981

Lung tumor tissue from five patients and normal peripheral lung tissue from the same patients was treated in culture with 20 uM labeled 1-naphthol. After incubation, culture medium was analyzed for glucuronide and sulfate conjugates by thin layer chromatography. Radioactivity retained in the medium accounted for 70-90% of the original amount added. Unmetabolized 1-naphthol in the medium varied from 37.7-91.9% for normal lung tissue and from 55.9-99.0% for tumor tissue. The primary metabolite formed by normal tissue was 1-naphthyl sulfate (1-NS: 6.4-59.9%), with no detectable 1-naphthyl glucuronide (1-NG). The primary metabolite formed by tumor tissue was 1-NG (0.3-39.8%), with little or no 1-NS (0.7-1.0%). Tumor tissue from one patient formed no detectable conjugates of either type. Evidently tumorigenesis is accompanied by the appearance of a conjugation system that has little or no activity in normal host lung tissue. This may have significance in the exploitation of biochemical differences between normal and tumor tissues for production of selective chemotherapeutic effects on cancer cells. (5 Refs)

8. GLUCURONIC ACID AND SULPHATE ESTER CONJUGATION IN HUMAN LUNG CANCER CELL LINES.

Gibby EM, Mehta R, Ellison M, Cohen GM
Div. Toxicology, Dept. Biochemistry, Univ. Surrey, Guildford, Surrey GU2 5XH, England
Biochem Soc Trans; 9(1):111 1981

Eight cell lines derived from human lung tumor tissue were incubated with radioactively-labeled 1-naphthol (1-N: 10 uM) or hydroxybenzo[a]pyrene (HBP: 2 uM) for 90 min. Conjugates of 1-N and HBP in the culture medium were analyzed by thin-layer chromatography. Generally 1-N was metabolized to a greater extent than HBP. Four of the cell lines formed the glucuronide conjugate (GC) of 1-N. Two of these cell lines formed GC extensively and exclusively. Three cell lines did not metabolize 1-N. One produced only the sulfate conjugate (SC). The GRi and Ben cell lines, derived from poorly-differentiated epidermoid carcinomas, produced more GC [3.93 and 16.65 nanomoles/mg protein/90 min (nm/mg/t), respectively] than SC (less than 0.01 nm/mg/t for both lines). Results with HBP were similar for the two lines, but at lower rates (0.03 and 0.20 nm/mg/t, respectively). E14, derived from squamous cell carcinoma, and Poc and Mar, derived from oat-cell tumors, produced little or no conjugate of either type. Min, derived from adenocarcinoma, produced more GC (6.31 nm/mg/t) than SC (1.07 nm/mg/t). Mor, derived from anaplastic tumor, produced more GC (2.89 nm/mg/t) than SC (1.19 nm/mg/t). Dre, also from anaplastic tumor, produced more SC (0.95 nm/mg/t) than GC (0.01 nm/mg/t). Lack of SC production in some lines may be due to absence of sulfotransferase or inability to form a sulfate donor. Evidently different cell lines follow different patterns of conjugation. (2 Refs)

MODIFICATION OF CARCINOGEN METABOLISM

9. BIOCHEMICAL MECHANISM OF MODULATION OF SKIN CARCINOGENESIS BY RETINOIDS.

Verma AK
McArdle Lab. for Cancer Res., Univ. Wisconsin Medical Center, Madison, WI, 53706
Retinoids: Advances in Basic Research and Therapy, Proceedings of the International Dermatology Symposium held in Berlin, W. Germany, 13-15 October, 1980. Orfanos CE, Braun-Falco O, Farber EM, Grupper C, Polano MK, and Schuppli R, ed. Berlin, Springer-Verlag, 527 pp., 1981.

Investigations of mechanisms involving retinoids in the two-stage model of mouse skin carcinogenesis are reviewed. Application of retinoic acid (RA) 1 hr before application of 12-O-tetradecanoylphorbol-13-acetate (TPA) led to inhibition of induction of ornithine decarboxylase (ODC) and resultant putrescine accumulation, and inhibition of enhanced DNA synthesis at 18 hr, but not at 24 or 48 hr. RA did not inhibit S-adenosylmethionine decarboxylase induction, incorporation of [3H]leucine or [3H]histidine into epidermal protein, induction of cyclic AMP phosphodiesterase activity, accumulation of prostaglandins E and F, or hyperplasia occurring 1 or 3 days after TPA treatment. No increase in polyamine biosynthesis was detected after topical skin treatment with 17 nanomole RA, but incorporation of [3H]thymidine increased at 42 hr. RA inhibited skin papillomas and carcinomas when administered with TPA treatments, but not when given with initiating doses of 7,12-dimethylbenz[a]anthracene (DMBA) after repeated

TPA doses. RA did not promote growth of DMBA-induced tumors. Combined RA and DMBA treatment did not result in inhibition of induction of ODC or tumors. (58 Refs)

10. BIOLOGICAL EFFECTS OF RETINOIDS.

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Retinoids: Advances in Basic Research and Therapy, Proceedings of the International Dermatology Symposium held in Berlin, W. Germany, 13-15 October, 1980. Orfanos CE, Braun-Falco O, Farber EM, Grupper C, Polano MK, and Schuppli R, ed. Berlin, Springer-Verlag, 527 pp., 1981.

The final paper presents a summary and conclusions of the meeting. Comments are presented on many subjects including transport, metabolism, side effects, teratogenicity, mutagenicity, effect on epithelial proliferation, differentiation, tumor growth, immunity and antiinflammatory effects of retinoids. (no Refs)

11. BETA-NAPHTHYLISOTHIOCYANATE-INDUCED ALTERATIONS IN HEPATIC DRUG METABOLISM AND LIVER MORPHOLOGY.

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Toxicol Appl Pharmacol; 60(3):527-534 1981

The effects of continuous feeding with beta-naphthylisothiocyanate (BNIT: 0.022%, 0.047%, or 0.1% of diet for 4 wk) on liver histology and hepatic enzymes were studied in male Charles River F-344 rats. Rats fed 0.1% BNIT developed multifocal granulomatous inflammatory lesions, but the lesions did not alter SGPT or serum bilirubin levels. BNIT treatment resulted in a dose-dependent increase in hepatic cytochrome P-450, benzphetamine-N-demethylase, and ethoxycoumarin-O-deethylase activity. BNIT also stimulated DT-diaphorase activity, but it did not alter epoxide hydrolase activity assayed with benzo(a)pyrene-4,5-oxide or styrene oxide as substrates. These effects contrast markedly with those of alphanaphtylisotiocyanate. which also inhibits chemically induced hepatocarcinogenesis. Stimulation of mixed-function oxidases and DT-diaphorase may be a factor in the anticarcinogenic action of BNIT. (36 Refs)

12. EFFECTS OF PHENOBARBITAL PRETREATMENT ON THE METABOLISM AND TOXICOKINETICS OF AFLATOXIN B1 IN THE RHESUS MONKEY.

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Toxicol Appl Pharmacol; 60(3):387-397 1981

Five male rhesus monkeys were treated with phenobarbital (PB: 15 mg/kg, 2 x/day) for 1 wk prior to administration of aflatoxin B1 (AFB1: 0.1-1.0 mg/kg, iv). PB pretreatment enhanced the in vitro conversion of AFB1 to aflatoxin Q1 and aqueous metabolites in monkey liver. Although PB did not appreciably alter the rate or vol of AFB1 distribution in vivo, it reduced plasma levels of total aflatoxins, AFB1, and the toxic metabolite aflatoxin M1 (AFM1). Decreased AFM1 levels and increased levels of less toxic water-soluble metabolites were found in the urine of PB-treated monkeys. These findings demonstrated that increased hepatic AFB1 metabolism results in elimination and circulation os less toxic, less mutagenic, and highly excretable metabolites. (49 Refs)

13. EFFECT OF PHENOBARBITAL PRETREATMENT ON THE TOXICITY AND METABOLISM OF 2,4-DIAMINOANISOLE.

Ruchirawat M, Grantham PH, Benjamin T, Weisburger EK
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Biochem Pharmacol; 30(19):2715-2718 1981

The effects of phenobarbital (PB) on the acute toxicity, macromolecular binding, disposition, and metabolism of 2,4-diaminoanisole (2,4-DAA) were studied in young male Fischer rats. At 5 and 24 hr after ip injection of [14C]-2,4-DAA, the highest concentration in control and PB-pretreated animals occurred in the kidney. Lower levels were found in the liver, spleen, lung, heart, and testis, respectively. The higest concentration of 2,4-DAA bound to tissue macromolecules was found in the kidney, followed by the liver, spleen, lung, heart, and testis, respectively. Concentrations of bound materials at 24 hr were approx half of those observed at 5 hr. Pretreatment with PB significantly increased binding, but only in the liver and kidney and not in other organs. In control rats, who received equal vol of NaCl and [14C]-2,4-DAA, 31% of the 14C dose was found in the urine in 5 hr, and 69% by 24 hr. In PB-pretreated rats, the rate of excretion of radioactivity was somewhat faster than that of the control animals: 42% of the radioactivity was in the urine at 5 hr. No difference in the excretion of total radioactivity or of the radioactivity in each fraction was observed between the PB-pretreated and control groups at the 24 hr period. The high pressure liquid chromatography separation of the five known metabolites of 2,4-DAA in control and PB-pretreated rats is described. The acute toxicity of 2,4-DAA was increased by PB treatment as evidenced by a change in the LD50 dose from 116 mg/kg to 97 mg/kg in the PB-pretreated rats. The mechanism and implications of the PB-related effects on 2,4-DAA metabolism are discussed. (14 Refs)

14. HUMAN SALIVA INACTIVATES MUTAGENICITY OF CARCINOGENS.

Nishioka H, Nishi K, Kyokane K
Div. Biochemistry, Doshisha Univ., Kyoto, Japan
Mutat Res; 85(5):323-333 1981

Various carcinogens, suspected carcinogens, certain pyrolysates (beef, salmon, sodium glutamate, polypeptone), and cigarette smoke condensate (CSC) were incubated with human saliva from healthy subjects. Effects on mutagenicity were tested in a modified Ames test with Salmonella typhimurium strains TA 98 and TA 100. Metabolic activation for development of mutagenicity was required by aflatoxin B1, benzo(a)pyrene (BP), tryptophan pyrolysate-1 (Tr-P-1, isolated from boiled beef), the other pyrolysates, and CSC. No metabolic activation was required by 2-(2-furyl)-3-(5-nitro-2-furyl)acrylamide (AF-2; a nitrofuran used as a food additive during 1966-1975 in Japan), N-methyl-N'-nitro-N-nitrosoguanidine (MNNG), methyl methanesulfonate (MMS), 4-nitroquinoline 1-oxide (4NQO) and quercetin. Saliva inactivated AF-2, MNNG, 4NQO, aflatoxin B1, BP, and Trp-P-1. Mutagenic activities of quercetin, pyrolysates of beef, salmon, and sodium glutamate, and CSC decreased to some extent; the activities of MMS and polypeptone pyrolysate were not affected. Boiled saliva inactivated AF-2 somewhat in TA 98 but not in TA 100 cultures. Complex mechanisms may be involved in the inactivation of mutagenicity of carcinogens by saliva. (22 Refs)

MUTAGENICITY OF ACTIVATED METABOLITES OF CARCINOGENS

15. INFLUENCE OF MICROSOMAL AND CYTOSOLIC FRACTIONS FROM RAT, MOUSE, AND HAMSTER LIVER ON THE MUTAGENICITY OF DIMETHYLNITROSAMINE IN THE SALMONELLA PLATE INCORPORATION ASSAY.

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Cancer Res; 41(11,part1):4361-4367 1981

Dimethylnitrosamine (DMN) was mutagenic in the Salmonella plate incorporation assay (Ames test) at a level of 10 umol/plate (3.7 mM) in the presence of hamster liver S-9. Mutagenicity of DMN at this level was not observed when the S-9 was derived from mouse or rat liver, although the mouse liver and hamster liver S-9 had similar DMN demethylase activities. Both mouse and rat liver S-9 inhibited the mutagenicity of DMN mediated by hamster liver S-9; the inhibitory factor was contained in the microsomal fraction. Mouse or rat liver microsomes did not inhibit the DMN demethylase activity of hamster liver S-9. The microsomal inhibitor from rat or mouse liver was stable at 60 but was inactivated at 70 C. DMN demethylase from both rat and mouse liver was inactivated at 60 C. Although the DMN demethylase activity of hamster liver S-9 was contained in the microsomal fraction, DMN mutagenesis under conditions of the assay required the presence of both microsomal and cytosolic (S-105) fractions; the cytosols from hamsters, mice, and rats were all effective. The cytosolic factor required for DMN mutagenesis was sensitive to trypsin and was not dialyzable. The presence of an inhibitor of DMN activation in rat and mouse microsomes may account for, or contribute to, the failure of liver S-9 preparations from these species to activate DMN to a mutagen under standard conditions of the Ames test. The requirement for the cytosolic fraction may indicate that DMN demethylase is not sufficient for the activation of DMN to a mutagen under the conditions used in these studies. (Author abstract) (46 Refs)

16. GREATER EFFECTIVENESS OF HEPATOCYTE AND LIVER S9 PREPARATIONS FROM HAMSTERS THAN RAT PREPARATIONS IN ACTIVATING N-NITROSO COMPOUNDS TO METABOLITES MUTAGENIC TO SALMONELLA.

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JNCI; 67(5):1117-1122 1981

A comparison was made of the ability of liver S9 and hepatocyte preparations from noninbred Syrian golden hamsters and noninbred Sprague-Dawley rats to metabolically activate a number of nitroso compounds in the Salmonella mutagenesis assay. The liver S9 and hepatocyte preparations from hamsters were consistently more effective than were preparations from rats in metabolizing nitrosodimethylamine (NDM), nitrosodiethylamine, nitrosodiallylamine, nitrosopyrrolidine (NP), nitrosomorpholine (NM), nitrosodiethylmethylurea (NDEMU), and nitrosodimethylethylurea (NDMEU) to mutagenic forms. The use of hamster S9 preparations with NP and NM resulted in up to 14x the number of revertant colonies obtained with rat preparations; in the presence of hamster hepatocytes, up to 32x the number of revertants were obtained. The S9 preparations from male hamsters not treated with the enzyme inducers phenobarbital and Aroclor 1254 were more effective than were those from female hamsters for activating NP, NM, and NDM. NDEMU and NDMEU, which have been reported to be carcinogens but not mutagens, were mutagenic in the presence of induced liver S9 or hepatocyte preparations from hamsters but not from rats. When tested with any of the S9 or hepatocyte preparations, nitrosodiphenylamine and nitrosomethylaniline, also reported to be carcinogens but not mutagens, gave no mutagenic responses. Nitrosodioctylamine, which has been reported to be noncarcinogenic, was also not mutagenic. (Author abstract) (23 Refs)

17. ENHANCEMENT OF N-HYDROXY-2-AMINOFLUORENE BACTERIAL MUTAGENICITY BY THE SOLUBLE PROTEIN FRACTION FROM RAT LIVER AND PARTIAL PURIFICATION OF THE ENHANCEMENT ACTIVITY.

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Cancer Res; 41(11,part1):4600-4605 1981

Bacterial mutagenesis from 2-aminofluorene mediated by washed rat liver microsomes was elevated 2-to 3-fold by addition of the hepatic soluble protein fraction. Enhancement was observed at 2-aminofluorene concentrations between 1 and 20 ug/assay but not at 30 to 50 ug/assay. The soluble protein fraction (without added microsomes) did not activate 2-aminofluorene for bacterial mutagenesis. However, mutagenesis by N-hydroxy-2-aminofluorene or 2-nitrosofluorene was enhanced by the soluble protein fraction, but only when reduced nicotinamide adenine dinucleotide phosphate was also present. On the basis of chemical assay, reduced nicotinamide adenine dinucleotide phosphate reduced 2-nitrosofluorene to N-hydroxy-2-aminofluorene and protected the hydroxylamine from oxidation, thus indicating that it was the mutagenicity of N-hydroxy-2-aminofluorene (but not 2-nitrosofluorene) which was enhanced by the soluble protein fraction. Without the added soluble protein fraction, mutagenesis by N-hydroxy-2-aminofluorene or 2-nitrosofluorene was unaffected by reduced nicotinamide adenine dinucleotide phosphate. We succeeded in partially purifying a protein fraction with properties of the enhancement activity. The partially purified fraction, which represents a 14-fold increase in specific activity, was assigned a mol wt of 33,500 by gel filtration through Sephadex G-100. This fraction was resolved into three components by polyacrylamide gel electrophoresis; the mol wt of the three components were determined by sodium dodecyl sulfate-polyacrylamide gel (10%) electrophoresis to be 33,000, 27,000, and 16,250. The mechanism of mutagenesis enhancement remains unknown. (Author abstract) (27 Refs)

18. MUTAGENICITY OF ISOMERIC BETA, GAMMA, GAMMA-UNSATURATED N-NITROSAMINES DERIVED FROM TERPENE ALKANOLAMINES.

Abidi SL, Finch RA
P. O. Box 65, La Crosse, WI, 54601
Environ Mutagen; 3(5):587-591 1981

The Ames Salmonella/microsome mutagenicity test was performed on a 1:2 mixture of cis-N-nitroso-2(3',7'-dimethyl-2',6' octadienyl)aminoethanol (cis-NDOA) and trans-N-nitroso-2(3',7'-dimethyl-2',6' octadienyl)aminoethanol (trans-NDOA). With the cis,trans-NDOA mixture, tested at dose levels of 50, 100, and 250 ug/incubation mixture (IM), without S-9 activation, no significant increase in the number of revertant colonies/plate was seen in any of the tester strains and no dose-response relationship was noted. At doses of 50o and 100 ug/IM in the presence of S-9 activation, significantly greater numbers of revertant colonies were noted only in tester strains TA100 and TA1535. A cytotoxic effect was noted in all the tester strains at a dose level of 250 ug/IM. A slight cytotoxic effect was noted in strain TA1535 at a dose level of 100 ug/IM. It was concluded that under the conditions of the test, the mixture of cis and trans isomers of NDOA is mutagenic for the Salmonella tester strains TA100 and TA1535 in the presence of Aroclor 1254-induced rat liver S-9 activation system. (6 Refs)

19. INDUCTION OF SISTER CHROMATID EXCHANGES AND CHROMOSOME ABERRATIONS IN CULTURED MAMMALIAN CELLS BY N-NITROSOCIMETIDINE.

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Cancer Lett; 14(1):71-75 1981

The possibility that N-nitrosocimetidine (NC), formed by the nitrosation of cimetidine (used in the treatment of gastric disorders), induces sister chromatid exchanges (SCE) and chromosomal aberrations in cultured Chinese hamster ovary cells (CHO) was investigated. NC caused a concentration-related increase in both SCE and chromosome aberrations in a concentration as low as 1.2 x 10(-7) M. At a concentration of 1.2 x 10(-4) M the number of SCE was too great to allow accurate counting and chromosome aberrations were induced in more than 90% of the metaphases. The chromosome aberrations observed were all of the chromatid type. On a molar basis, NC was approx two-thirds as potent an inducer of SCE as the gastric carcinogen N-methyl-N'-nitro-N-nitrosoguanidine. These findings constitute further evidence that NC possesses carcinogenic activity. (10 Refs)

20. STRUCTURAL BASIS OF THE MUTAGENICITY IN BACTERIA OF NITRATED NAPHTHALENE AND DERIVATIVES.

McCoy EC, Rosenkranz EJ, Petrullo LA, Rosenkranz HS, Mermelstein R
Center for Environmental Health Sciences, Case Western Reserve Univ. Sch. Medicine, Cleveland, OH, 44106
Environ Mutagen; 3(5):499-511 1981

The mutagenic activity of nitronaphthalenes and some of their derivatives was investigated in the Salmonella mutagenicity assay. The 2-nitro and 2-hydroxylaminonaphthalenes were more mutagenic than their corresponding 1-substituted analogs. The adducts induced by 1-nitronaphthalene differed chemically from those derived from the 2-nitro analog. For expression of the mutagenic action of these chemicals, r eduction of the chemicals to the corresponding hydroxylamines was required. These differences in mutagenic responses may be due to the different DNA adducts that have been identified after reaction of hydroxylaminonaphthalenes with DNA. The nitroso-containing polycyclic chemicals might not derive their mutagenic activity from reduction to the corresponding hydroxylamines. If there is a relationship between mutagenicity in Salmonella and human risks, adjusting the conditions for combustion in engines such that extensive nitration is favored may decrease the emission of hazardous substances. On a molar basis, when a mutagen is capable of inducing frameshift mutations by adduct formation as well as by simple intercalation, then the activity induced by the adduct greatly exceeds the activity due to simple intercalators. While bicyclic 2-nitronaphthalene and 4-nitroquinoline-1-oxide and their metabolites are primarily base-substitution mutagens, the introduction of a third ring structure results in a different mutational mechanism leading to frameshift mutagens. (58 Refs)

21. SPECIES DIFFERENCE IN N-HYDROXYLATION OF A TRYPTOPHAN PYROLYSIS PRODUCT IN RELATION TO MUTAGENIC ACTIVATION.

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Cancer Res; 41(11,part1):4518-4522 1981

Metabolic activation of a tryptophan pyrolysate, 3-amino-1-methyl-5H-pyrido[4,3-b]indole (Trp-P-2), in liver microsomes from rats, mice, hamsters, guinea pigs, and rabbits was studied to know whether N-hydroxylation is a common obligatory step for mutagenic activation of Trp-P-2. Among hepatic microsomes obtained from untreated animals, the highest activity of Trp-P-2 N-hydroxylase was observed in microsomes from hamsters, followed by those from guinea pigs, mice, and rabbits. In rats, the activity was low, and there was no appreciable difference between the sexes. The activity of Trp-P-2 N-hydroxylase in microsomes was increased by pretreating the animals with a polychlorinated biphenyl mixture. The induction was most profound in rats, and the activity was enhanced 257-fold, as compared to that of untreated animals. The activity was also enhanced in microsomes from polychlorinated biphenyl mixture-treated rabbits, mice, and hamsters, while the activity was increased only slightly in guinea pigs and was thereby lowest among microsomes from the polychlorinated biphenyl mixture-treated animals. In bacterial mutagenesis test systems using Salmonella typhimurium TA 98, the number of revertants induced by Trp-P-2 was increased in parallel with the microsomal ability of the N-hydroxylation. These results indicate that in all species examined N-hydroxylation is an essential metabolic step for mutagenic activation of Trp-P-2. (Author abstract) (32 Refs)

22. THE MUTAGENIC EFFECT OF CIS-DIAMMINEDICHLOROPLATINUM II AND ITS DEGRADATION PRODUCTS IN THE AMES MICROBIAL ASSAY.

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Environ Mutagen; 3(5):555-563 1981

The Ames microbial mutagenicity assay was used to test the mutagenicity of cis-diamminedichloroplatinum (II) (cis-DDP) and its degradation products (obtained from a soln aged for 12 mo at 37 C), platin B salt, magnus red, and magnus red anion salt in order to determine if the positive mutagenic response of the platinum compound could be due to, or enhanced by, the presence of degradation products. A significant increase in hist+-revertants occurred with Salmonella strains TA98, TA100, TA92, and TA94 with platin B salt, magnus red, magnus red anion salt, and lyophilized cis-DDP. The aged cisplatin, however, exhibited an increase only with strains TA100, TA92, and TA94. All degradation products exhibited a slight but significant mutagenic effect with strains TA1535 and TA1537. The mixed function oxidase activation system was required for mutagenicity only in the positive control ethidium bromide. These results indicate that platinum degradation complexes are weak mutagens which can induce both base pair and frameshift-type mutations. (32 Refs)

23. POTENCY OF SOME CARBAMATES AS MULTIPLE TISSUE SISTER CHROMATID EXCHANGE INDUCERS AND COMPARISON WITH KNOWN CARCINOGENIC ACTIVITIES.

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Cancer Res; 41(11,part1):4489-4492 1981

The ethyl, ethyl N-hydroxy, isopropyl, and methyl esters of carbamic acid were examined for their abilities to induce sister chromatid exchanges (SCEs) in alveolar macrophages, bone marrow, and regenerating liver cells of C57BL/6J x DBA/2J F1 mice. The relative potencies in inducing SCE, ethyl greater than ethyl N-hydroxy- greater than isopropyl, paralleled previously described activities for induction of lung adenomas in strain A mice. The noncarcinogenic methyl carbamate was inactive in the SCE assay. Relative to bone marrow, regenerating liver and alveolar macrophage cells demonstrated increased susceptibility to carbamate-induced SCE. Of all carbamates studied, only the directly active compound, ethyl N-hydroxycarbamate, produced distinctly different responses in extrahepatic tissues of hepatectomized and intact mice. In intact mice, SCE levels induced by ethyl carbamate in bone marrow and alveolar macrophage cells were not significantly different whether assay followed the last of 12 (3x weekly) serial injections of 2.2 mmol/kg each or after a single injection of 2.2 mmol/kg. Linear regression relationships of log ethyl carbamate versus log SCE or log adenoma response were found to be parallel with the two assays having similar sensitivities. (Author abstract) (21 Refs)

24. SISTER CHROMATID EXCHANGE (SCE) AND STRUCTURAL CHROMOSOME ABERRATION IN MUTAGENICITY TESTING.

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Hum Genet; 58(3):235-254 1981

An objective analysis is presented of data gained so far relative to the value in mutagenicity testing of sister chromatid exchange (SCE) and classical chromosome aberration (CA) analysis. Detailed studies are reported on spontaneous SCE and chromosome damage in normal cells, and in cells of patients with genetic and neoplastic disease. Qualitative results on SCE induction and CA are presented relative to radiation, chemicals, chromosomal breakage syndromes and virus. Quantitative results are presented on potent inducers of SCE and break aberrations, substances inducing SCE but not breaks in the same test system, and clastogens with no or minor SCE-inducing activity. A section deals with modification of SCE and chromosome breakage: clastogens and anticlastogens. A discussion of molecular aspects of SCE induction and breakage involves consideration of evidence for the primary lesions leading to SCE formation, role of replication and involvement of repair mechanisms. These studies indicate SCE and structural CA are two largely different cytogenetic endpoints of mutagenic action. It is suggested that the SCE-technique is a valuable additional method for cytogenetic testing, which, however, is not adequate to replace the classical methods of analysis of structural chromosome damage. (165 Refs)

25. CARCINOGEN BIOASSAY AND MUTAGENICITY STUDIES WITH THE HYPOLIPIDEMIC AGENT GEMFIBROZIL.

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JNCI; 67(5):1105-1116 1981

Gemfibrozil, a novel hypolipidemic agent identified chemically as 2,2-dimethyl-5-(2,5-xylyloxy)valeric acid, was evaluated for mutagenic potential in in vitro assays with Salmonella typhimurium. For evaluation of tumorigenic potential, gemfibrozil was administered in the diet (0, 30, and 300 mg gemfibrozil/kg) to groups of noninbred CD-1 mice (72/sex) and noninbred CD rats (50/sex) for 78 and 104 wk, respectively. In the bacterial mutagenesis assays, between 100 and 2,500 ug gemfibrozil/plate failed to induce a significant increase in revertant bacterial colonies. Neither was a mutagenic response in bacterial assays induced at concentrations up to 300 ug of five in vivo metabolites of gemfibrozil isolated from rat urine/plate. In mice, gemfibrozil did not significantly increase the frequency or the mean latency period of tumors. In rats, the statistically significant increases in hepatocellular tumors and interstitial cell tumors of the testes were dose related. Adrenal medullary and pancreatic acinar tumors were increased in male rats but were inversely dose related. Under the conditions of this assay, gemfibrozil did not elicit a tumorigenic potential in mice and female rats. In male rats and related to the hepatocellular tumor response, the peroxisome proliferation seen did not occur in humans chronically administered hypolipidemics. (Author abstract) (22 Refs)

BINDING OF CARCINOGENS AND THEIR METABOLITES TO MACROMOLECULES

26. NUCLEAR UPTAKE AND SUBSEQUENT NUCLEAR METABOLISM OF BENZO(A)PYRENE BINDING TO CYTOSOLIC PROTEINS.

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Cancer Res; 41(11,part1):4408-4414 1981

The binding of [3H]benzo(a)pyrene to proteins of rat liver cytosol, the nuclear uptake of cytosolic protein-bound [3H]benzo(a)pyrene, and the subsequent nuclear metabolism of the polycyclic hydrocarbon were investigated. The binding of [3H]benzo(a)pyrene to cytosol had a saturable high affinity component with a Kd of 2.54 nM and a capacity of 530 fmol/mg protein. Specific binding of [3H]benzo(a)pyrene to cytosol was also assayed using sucrose density gradient analysis. Nuclear uptake of protein-bound [3H]benzo(a)pyrene was demonstrated both directly and by sucrose density gradient analysis. The nuclear benzo(a)pyrene was readily converted to metabolites which were qualitatively and quantitatively no different from nuclear metabolites of exogenously (not protein associated) added [3H]benzo(a)pyrene. (Author abstract) (42 Refs)

27. INHIBITION IN VIVO OF THE FORMATION OF ADDUCTS BETWEEN METABOLITES OF BENZO(A)PYRENE AND DNA BY BUTYLATED HYDROXYANISOLE.

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Cancer Res; 41(11,part1):4309-4315 1981

Antioxidants have been shown to inhibit the carcinogenic effects of a variety of chemical carcinogens. For example, the phenolic antioxidant butylated hydroxyanisole (BHA) has been shown to be a potent inhibitor of benzo(a)pyrene (BP)-induced neoplasia in mouse lung and forestomach. The objective of the present study was to determine whether or not BHA, under conditions known to result in inhibition of BP-induced neoplasia, affects the formation of BP metabolite:DNA adducts. Following po administration of a carcinogenic dose of [3H]BP to A/HeJ mice, radioactivity was detected in the DNA of both lung and liver. Analysis of the deoxyribonucleosides by high-pressure liquid chromatography showed that the major adduct in both tissues cochromatographed with the (+-)-7beta, 8alpha-dihydroxy-9alpha,10alpha-epoxy-7,8,9,10 tetrahydrobenzo(a)pyrene (BPDEI):deoxyguanosine adduct. The 7beta,8alpha-dihydroxy-9beta,10beta-epoxy-7,8,9,10 tetrahydrobenzo(a)pyrene (BPDEII):deoxyguanosine adduct was 10 to 15% of the BPDEI adduct in both lung and liver. Another adduct, possibly derived from BP phenol(s), was also detected in lung and was 10 to 20% of the BPDEI adduct. Treatment of animals with BHA decreased the amount of the BPDEI adduct in the lung and the liver approx 55 and 75%, respectively. The decrease in the amount of this adduct in the lung appears to correlate with the inhibition of pulmonary adenoma formation. Thus, BHA appears to inhibit BP-induced pulmonary adenoma formation by inhibiting the amount of the BPDE:DNA adducts formed in lung. Possible mechanisms by which BHA treatment inhibits the formation of BPDE:DNA adducts are discussed. (Author abstract) (44 Refs)

28. DOSE-DEPENDENCY OF 2-ACETYLAMINOFLUORENE BINDING TO LIVER DNA AND HEMOGLOBIN IN MICE AND RATS.

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Toxicol Appl Pharmacol; 60(3):472-478 1981

Binding of 2-acetylaminofluorene (2-AAF) to liver DNA and Hb in Sprague-Dawley rats and CD-1 mice of both sexes was determined to test proposals that Hb binding correlates with target organ DNA binding and carcinogenicity. In both species, 2-AAF binding to liver DNA and HB increased as a linear function of dose (1-100 umoles/kg, po). This indicated that the formation of reactive 2-AAF liver metabolites also was linearly related to dose. No sex difference was observed in 2-AAF macromolecular binding, except for an apparent higher liver DNA binding in female mice than in male mice. DNA binding was only 7x greater and Hb binding only 2.5x greater in rats than mice; thus the binding did not reflect the 246x greater carcinogenicity of 2-AAF in rat liver. The results indicated that Hb binding can be used to predict DNA binding and the systemic dose; however, the extent of DNA binding does not predict carcinogenic potency. (20 Refs)

29. ADDUCTS FROM THE REACTION OF O,O'-DIACETYL OR O-ACETYL DERIVATIVES OF THE CARCINOGEN 4-HYDROXYAMINOQUINOLINE 1-OXIDE WITH PURINE NUCLEOSIDES.

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(c/o Loucheux-Lefebvre) Institut Recherches le Cancer de Lille et Unite, 124 de l'INSERM, BP 311, 59020 Lille Cedex, France
Cancer Res; 41(11,part1):4559-4565 1981

The diacetyl derivative of 4-hydroxyaminoquinoline 1-oxide (4-HAQO), the proximate carcinogen of 4-nitroquinoline 1-oxide, was reacted in vitro with purine nucleosides to give five adducts (3 with guanosine and 2 with adenosine). The same nucleoside modifications were also obtained with a monoacetyl derivative of 4-HAQO which is probably 4-acetoxy-aminoquinoline 1-oxide. The structure of the major adduct (the so-called dG III) was identified as N-(deoxyguanosine-C8-yl)-4-aminoquinoline 1-oxide. The isolation of this adduct from the 4-HAQO-modified DNA in vivo provides strong support for the hypothesis that the acetyl derivatives of 4-HAQO constitute a good model for the ultimate carcinogen. (Author abstract) (21 Refs)

30. ROLES OF 2-HALOETHYLENE OXIDES AND 2-HALOACETALDEHYDES DERIVED FROM VINYL BROMIDE AND VINYL CHLORIDE IN IRREVERSIBLE BINDING TO PROTEIN AND DNA.

Guengerich FP, Mason PS, Stott WT, Fox TR, Watanabe PG
Dept. Biochemistry, Center Environmental Toxicology, Vanderbilt Univ. Sch. Medicine, Nashville, TN, 37232
Cancer Res; 41(11,part1):4391-4398 1981

The metabolism of [1,2-14C]vinyl bromide (VBR) to products irreversibly bound to DNA and protein was examined in rat liver microsomes, reconstituted cytochrome P-450 systems, and isolated hepatocytes. A role for cytochrome P-450 was confirmed using inhibition and reconstitution experiments. The major form of cytochrome P-450 involved in VBR metabolism does not appear to be either of the major isozymes induced by phenobarbital or beta-naphthoflavone, as determined by induction, reconstitution, and antibody inhibition studies. 2-Bromoethylene oxide and 2-bromoacetaldehyde, suspected metabolites of VBR, were synthesized and found to be substrates for rat liver epoxide hydrolase and equine liver alcohol dehydrogenase, respectively. These enzymes were used to probe the roles of the two possible metabolites in the irreversible binding of products of VBR to protein and DNA. Alcohol dehydrogenase was more effective than epoxide hydrolase in inhibiting the binding of VBR metabolites to protein in microsomal incubations. Epoxide hydrolase was effective in inhibiting the binding of VBR or vinyl chloride metabolites to calf thymus DNA added to such systems, but alcohol dehydrogenase was not. Similar results were obtained for binding of VBR metabolites to DNA in a reconstituted enzyme system. Reduced glutathione blocked nonenzymatic binding of 2-bromo[1,2-14C]acetaldehyde to protein but not DNA. Binding of vinyl chloride and VBR metabolites to protein was blocked by reduced glutathione, but binding to DNA was not. These results are consistent with the view that 2-haloethylene oxides are the major alkylating agents bound to DNA, and 2-haloacetaldehydes are the major alkylating agents bound to proein in these experimental systems. Studies with labeled 2-bromoacetaldehyde indicate that the slow kinetics of DNA binding by this compound is responsible in part for this phenomenon. Studies with isolated rat hepatocytes suggest that a significant portion of the total and reactive metabolites are able to leave these cells. In these systems, binding of metabolites of vinyl chloride to DNA outside the hepatocytes could be partially blocked by epoxide hydrolase or by alcohol dehydrogenase, implying that, as targets farther away from sources of reactive species are considered, the stabilities of these species become more important for reaction with nucleophilic sites. (Author abstract) (36 Refs)

ALTERATION OF MIXED FUNCTION OXIDASES BY CARCINOGENS

31. ELLIPTICINES AND HUMAN LIVER MICROSOMES: SPECTRAL INTERACTION WITH CYTOCHROME P-450 AND HYDROXYLATION. INHIBITION OF ARYL HYDROCARBON METABOLISM AND MUTAGENICITY.

Lesca P, Beaune P, Monsarrat B
Laboratoire de Pharmacologie, Toxicologie Fondamentales, 205 route de Narbonne, 31078 Toulouse Cedex, France
Chem Biol Interact; 36(3):299-309 1981

Some pharmacological properties of ellipticine (E) and its derivatives linked to their interaction with cytochrome P-450 have been investigated with human liver microsomes. 9-Hydroxyelipticine (9-OHE) interacts with human liver•cytochrome P-450 exhibiting a Type II spectrum (lambdamax:428 nm, Ks = 1.1 uM). After incubation with human liver microsomes the E was converted to 9-OHE; 7-hydroxyellipticine was not produced. The cytotoxic effect of this biotransformation has been evaluated on leukemic L1210 cells, in vitro, and found to be equal to those elicited by liver microsomes of control or phenobarbital (PB) pretreated rats. Moreover, 9-OHE and 9-fluoroellipticine (9-FE) strongly inhibit the benzo[a]pyrene hydroxylase (AHH) activity of human liver microsomes (I50 = 2.6 uM and 1.6 uM, respectively) as well as the mutagenesis induced by the polycyclic aromatic hydrocarbon 2-acetylaminofluorene (AAF); 1 ug/plate of each of these compounds is able to inhibit by more than 50% the mutagenicity of 5 ug/plate AAF. (Author abstract) (29 Refs)

32. DIFFERENTIAL EFFECT OF SEVERAL INDUCERS ON HEPATIC AND MAMMARY BENZO(A)PYRENE METABOLISM IN RAT AND HAMSTER.

Gingell R, Weber A, Ilacqua V, Van de Walle C, Hertzog P
Shell Development Co., Westhollow Res. Center, P. O. Box 822, Houston, TX, 77001
Drug Chem Toxicol; 4(2):101-112 1981

The ability of female Sprague Dawley rat and Syrian golden hamster mammary microsomes, as compared with the liver, to metabolize benzo(a)pyrene (BP) was examined in an attempt to understand the different susceptibilities of these species to polynuclear hydrocarbon-induced mammary tumorigenesis. The effect of pretreatment with several known mixed function oxidase inducers on these activities was studied in both species. Control hamster hepatic benzo(a)pyrene-hydroxylase (BPH) activity was considerably greater than that of the rat. Aroclor was the only inducer to significantly increase hamster hepatic BPH activity, and this by only two-fold. 7,12-dimethylbenz(a)anthracene and 3-methylcholanthrene had no effect on hamster liver BPH activity while beta-naphthoflavone (BNF) slightly inhibited this activity. All compounds examined were potent inducers of hepatic BPH and cytochrome P450 in the rat. Control hamster mammary microsomal BPH activity was much lower than the hepatic level, but was four-fold greater than the corresponding level for the rat. All the pretreatments caused similar increases in mammary activity in both species, BNF being the most effective. The ability of control hamster hepatic microsomes to metabolize BP was considerably greater than for the rat. The results indicated that rat and hamster mammary gland microsomes, as well as those of liver, are capable of metabolizing BP. All the pretreatments investigated induced mammary activity in both species, but the rat activity was more inducible than that of the hamster. It was therefore suggested that metabolic activation of carcinogenic polycyclic hydrocarbons can occur in the mammary gland itself. (16 Refs)

33. INDUCTION OF ARYLHYDROCARBON HYDROXYLASE AND BLAST TRANSFORMATION IN HUMAN BLOOD LYMPHOCYTES.

Fukuhara M, Bohuon C, Gharbi N, Biret F, Boudene C
Inst. Public Health, Shirokanedai, Minoto-ku, Tokyo, 108, Japan
Biochem Biophys Res Commun; 102(1):8-14 1981

The induction of arylhydrocarbon hydroxylase (AHH) by benzo(a)pyrene and the degree of blast transformation were measured simultaneously in peripheral hyman lymphocytes. While the induction ratio (induced:basal level) of AHH and induction ratio per unit of blast transformation varied at different culture times and at different phytohemagglutinin (PHA) concentrations for a particular individual, the ratio of absolute induced AHH activity and unit of blast transformation yielded a consistent value at different culture times and different PHA concentrations for the individual. AHH inducibility may be a useful parameter for the study of cancer susceptibility if inducibility is expressed in this new manner. (23 Refs)

34. 1,2-DIMETHYLHYDRAZINE-INDUCED CHANGES IN HEPATIC, SMALL INTESTINAL, AND COLONIC MUCOSAL CYTOCHROMES P-450 AND B5 OF RATS FED CITRUS PULP OR WHEAT BRAN.

Smith-Barbaro P, Hanson D, Reddy BS
Naylor Dana Inst. for Disease Prevention, Valhalla, NY, 10595
Drug Metab Dispos; 9(5):487-488 1981

A 3-mo feeding study showed that dietary fiber and the carcinogen 1,2-dimethylhydrazine interacted to alter hepatic and extrahepatic levels of cytochromes P-450 and b5 in liver, and small intestine and colon mucosa of male F344 rats. (16 Refs)

REVIEWS AND OTHER RELEVANT STUDIES

35. CARCINOGEN TESTING: CURRENT PROBLEMS AND NEW APPROACHES.

Weisburger JH, Williams GM
American Health Foundation, Valhalla, NY, 10595
Science; 214(4519):401-407 1981

The classic procedures for testing potential carcinogens in animals have basically not changed in the past 50 yr. Considerable knowledge of the mechanisms of carcinogenesis has accrued in the last 20 yr, particularly concepts on the metabolic activation of chemicals to reactive electrophilic compounds that can interact with nucleophilic cell components including DNA. These developments, in turn, have yielded a framework for integrating into carcinogen testing the determination of genetic effects of chemicals. A systematic decision point approach to carcinogen testing has been developed which entails a sequential decision-making process as specific tests are performed and evaluated prior to initiation of higher order, more complex tests. Compared to conventional bioassays in rodents, this approach provides knowledge based on mechanisms of carcinogenesis, yields a substantial amount of data at minimal cost, and forms a solid base for eventual health risk assessment. (Author abstract) (34 Refs)

36. NITROSABLE DRUGS.

Ziebarth D
Zentralinstitut fur Krebsforschung der Akademie der Wissenschaften der DDR, Lindenberger Weg 80, DDR-1115 Berlin-Buch, E. Germany
Arch Geschwulstforsch; 51(7):587-595 1981

The nitrosation of 61 potentially nitrosable drugs available for po administration in East Germany was studied in vitro under simulated conditions of the human stomach. Nitrosation of 10/61 drugs (aminophenazone, ampicillin, clomipramine, desipramine, ethambutol, imipramine, noramidopyrine methanesulfonate, oxacillin, phenoxymethylpenicillin, and piperazine) was observed. Nitrosodimethylamine, the principal product of aminophenazone, and mononitrosopiperazine, the principal product of piperazine, were identified chemically among the nitrosation products of the drugs. Both metabolites are carcinogenic for several animal species. The nitrosation of 9/10 drugs were inhibited 80-100% by ascorbic acid, and that of ampicillin by 18.2%. The findings indicate that po administered drugs forming carcinogenic N-nitroso compounds should be replaced by non-nitrosable drugs, and other potentially nitrosable drugs should be formulated with ascorbic acid, if they are compatible with this vitamin. (33 Refs) (In GER)

37. THE ROLE OF METALS IN CARCINOGENESIS: BIOCHEMISTRY AND METABOLISM.

Jennette KW
Dept. Chemistry, Dartmouth Coll., Hanover, NH, 03755
Environ Health Perspect; 40:233-252 1981

A review is presented of the biochemistry and metabolism of inorganic species involved in carcinogenesis. Such species may have a role in transport across the cell membrane, enzymatic and chemical transformation of redox active inorganic species within the cell, coordination to cellular small molecules and macromolecules, and inhibition, activation or change of specificity of cellular enzymes by inorganic species. Oxide complexes are discussed with respect to enzyme interaction, metabolism, and mutagenicity. The role of divalent ions is examined. Oxyanions of V, Cr, Mo, As, and Se cross cell membranes; once inside the cell they may act as phosphate and/or sulfate analogs, inhibiting enzymes which catalyze phosphoryl o r sulfuryl transfer reactions. They may serve as alternate enzyme substrates, but they form ester products which are hydrolytically unstable and decompose readily in aqueous soln. The divalent ions of Be, Mn, Co, Ni, Cd, Hg, and Pb are stable forms which may mimic essential divalent ions such as Mg, Ca, Fe, Cu, or Zn. These ions may complex small molecules, enzymes, and nucleic acids so as to alter the normal activity of these species. Free radicals produced in the presence of these metal ions may damage critical cellular molecules. (216 Refs)

38. CHEMISTRY AND METABOLISM OF METALS RELEVANT TO THEIR CARCINOGENICITY.

Martell AE, Berlin M, Brubaker G, Eichhorn GL, Grotyh D, Jennette K, Petering H, Piscator M, Schubert J, Seven I
Texas A and M Univ., College Station, TX, 77843
Environ Health Perspect; 40:27-34 1981

The chemical reactions of metals leading to cancer are considered. Chemical factors in metal metabolism include oxyanions, thermodynamic effects and kinetic factors that determine speciation, the role of speciation in dose effect-response relationships, and membrane transport. Proposed models of carcinogenesis include direct reactions with DNA and indirect reactions. Directions for future research are recommended. (37 Refs)

39. RECENT RESEARCH ON NICKEL CARCINOGENESIS.

Sunderman FW
Dept. Lab. Medicine, Univ. Connecticut Sch. Medicine, Farmington, CT, 06032
Environ Health Perspect; 40:131-141 1981

Nickel carcinogenesis research since 1975 is reviewed, with emphasis on new experimental techniques for studying carcinogenesis in vivo and in vitro. The subjects covered include epidemiologic studies, clinical investigations, carcinogenicity tests in animals exposed to nickel compounds by different administration routes, x-ray diffractometry and radiotracer studies of alpha-Ni3S2 metabolism, electron microscope studies of alpha-Ni3S2-induced tumors, cytogenetic and tumor transplantation studies, effects of nickel compounds on DNA synthesis, cell culture studies, bacterial mutagenicity tests, and effects of metals on viral and bacterial DNA polymerase. Prospects for future research on nickel carcinogenesis are summarized. (82 Refs)

40. RELATIONSHIP BETWEEN METAL TOXICITY TO SUBCELLULAR SYSTEMS AND THE CARCINOGENIC RESPONSE.

Squibb KS, Fowler BA
Lab. Pharmacology, Natl. Inst. Environmental Health Sciences, P.O. Box 12233, Research Triangle Park, NC, 27709
Environ Health Perspect; 40:181-188 1981

Subcellular systems that influence ultimate cellular responses to toxic and carcinogenic metals are reviewed. They include the endoplasmic reticulum (microsomal enzyme systems and protein synthesis), nuclei, mitochondria, lysosomes, and cellular membranes. Cell membranes regulate carcinogen uptake; microsomal enzymes are responsible for carcinogen metabolism; mitochondria and lysosomes c an affect detoxification and storage of carcinogens; and nuclear DNA polymerases can repair carcinogen-induced damage. (102 Refs)

41. HISTORY OF CANCER INVESTIGATION.

Gomez P, Rosado A
Unidad de Investigacion Clinica, Centro Medico Nacional, IMSS, Av. Cuauhtemoc 330, Mexico 7, D.F., Mexico
Arch Invest Med (Mex); 12(3):361-375 1981

Important biological hypotheses of carcinogenesis are reviewed: the majority are concerned with alterations in cellular genetic material. Chemical, physical, and viral carcinogens and their actions on cell metabolism are presented. Carcinogenesis occurs through somatic mutation resulting from external and internal factors. Solving the cancer riddle depends on advances in molecular biology and genetics with respect to regulatory mechanisms of cell differentiation and genetic control of differentiated cells. (49 Refs)

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As an additional service to readers of carcinogenesis (CK series) CANCERGRAMS, each issue now provides a bibliography of review articles of interest to carcinogenesis researchers, selected from journals screened for that month's CANCERGRAMS.

CHEMICAL CARCINOGENESIS

1. CHEMICAL COMPOUNDS AND CANCER RISK.
Schramm T, Janisch W
Zentralinstitut fur Krebsforschung der Akademie der Wissenschaften der DDR, Lindenberger Weg 80, DDR-1115 Berlin, E. Germany
Arch Geschwulstforsch; 51(7):561-565 1981
In GER

2. THE CARCINOGENICITY OF ARSENIC.
Pershagen G
Dept. Environmental Hygeine, Karolinska Inst., Stockholm, Sweden
Environ Health Perspect; 40:93-100 1981

3. THE CARCINOGENICITY OF CHROMIUM.
Norseth T
Inst. Occupational Health, Gydas vei 8, Oslo 3, Norway
Environ Health Perspect; 40:121-130 1981

4. ROLE OF COBALT, IRON, LEAD, MANGANESE, MERCURY, PLATINUM, SELENIUM, AND TITANIUM IN CARCINOGENESIS.
Kazantzis G
TUC Centenary Inst. Occupational Health, London Sch. Hygiene and Tropical Medicine, Keppel St., London WC1E 7HT, England
Environ Health Perspect; 40:143-161 1981

5. RECENT RESEARCH ON NICKEL CARCINOGENESIS.
Sunderman FW
Dept. Lab. Medicine, Univ. Connecticut Sch. Medicine, Farmington, CT, 06032
Environ Health Perspect; 40:131-141 1981

6. ROLE OF CADMIUM IN CARCINOGENESIS WITH SPECIAL REFERENCE TO CANCER OF THE PROSTATE.
Piscator M
Dept. Environmental Hygiene, Karolinska Inst., S-104 01 Stockholm, Sweden
Environ Health Perspect; 40:107-120 1981

7. CHELATING AGENTS IN BIOLOGICAL SYSTEMS.
Schubert J
Dept. Chemistry, Univ. Maryland Baltimore County, Catonsville, MD, 21228
Environ Health Perspect; 40:227-232 1981

8. BENZENE AS A RISK FACTOR.
Stobbe H
Universitatsklinik fur Innere Medizin 'Theodor Brugsch', Bereich Medizin der Humboldt-Universitat, Schumannstrasse 20/21, DDR-1040 Berlin, E. Germany
Arch Geschwulstforsch; 51(7):575-578 1981
In GER

9. FORMALDEHYDE IN DENTISTRY: A REVIEW OF MUTAGENIC AND CARCINOGENIC POTENTIAL.
Lewis BB, Chestner SB
800-A Fifth Ave., Suite 503, New York, NY, 10021
J Am Dent Assoc; 103(3):429-434 1981

10. CARCINOGENICITY OF HYDANTOINS: DATA, HYPOTHESES, AND PUBLIC REVIEWS.
Scoville B, White BG
Natl. Inst. Neurological and Communicative Disorders and Stroke, NIH, Bethesda, MD, 20205
Psychopharmacol Bull; 17(3):195-197 1981

11. PHENOXY ACIDS, CHLOROPHENOLS, AND CANCER.
Hardell L, Eriksson M
Onkologiska kliniken, Regionsjukhuset, Umea, Sweden
Lakartidningen; 78(34):2862-2863 1981
In SWE

12. PHENOXY ACIDS: A BRIEF REVIEW OF THE POSSIBLE HYGIENIC EFFECTS.
Edling C
Yrkesmedicinska kliniken, Regionsjukhuset, Linkoping, Sweden
Lakartidningen; 78(34):2861-2862 1981
In SWE

DIETARY FACTORS IN CARCINOGENESIS

13. NUTRITIONAL MODULATION OF CANCER.
Nauss KM, Newberne PM
Dept. Nutrition and Food Science, Massachusetts Inst. Technology, Cambridge, MA, 02139
Cancer Detect Prev; 3(2):367-417 1981

14. FIBER CARCINOGENESIS: EPIDEMIOLOGIC OBSERVATIONS AND THE STANTON HYPOTHESIS
Harington JS
Cancer Res. Dept., Natl. Cancer Assoc. South Africa, P.O. Box 2000, Johannesburg 2000, South Africa
JNCI; 67(5):977-989 1981

EPIDEMIOLOGY, ETIOLOGY AND GENETIC ASPECTS OF HUMAN CANCER

15. EPIDEMIOLOGY.
Alderson MR
Dept. Epidemiology, Inst. Cancer Res., London, England
Recent Results Cancer Res; 78:1-19 1981

16. ATLAS OF CANCER MORTALITY IN THE PEOPLE'S REPUBLIC OF CHINA. AN AID FOR CANCER CONTROL AND RESEARCH.
Li JY, Liu BQ, Li GY, Chen ZJ, Sun XD, Rong SD
Dept. Cancer Epidemiology, Cancer Inst. Chinese Acad. Medical Sciences, 2, Yabao Lu, Chaoyang, Qu, Beijing, People's Republic of China
Int J Epidemiol; 10(2):127-133 1981

ENVIRONMENTAL AND OCCUPATIONAL FACTORS IN CARCINOGENESIS

17. SIXTH EAST GERMAN CANCER CONGRESS WITH INTERNATIONAL PARTICIPATION, BERLIN, MARCH 2-5, 1981.
Schramm T, Ebeling K, Schwarz R, Heise E, Glaser A, Tanneberger St, Anger G
No affiliation given
Arch Geschwulstforsch; 51(7):551-560 1981
In GER

18. EPIDEMIOLOGICAL STUDIES INTO THE POSSIBLE CARCINOGENICITY OF HAIR DYES.
Clemmesen J
(c/o P. Lohman), Medical Biological Lab. TNO., P.O. Box 45, 2280 AA Rijswijk, The Netherlands
Mutat Res; 87(1):65-79 1981

CELLULAR AND MOLECULAR MECHANISMS IN CARCINOGENESIS

19. THE ROLE OF METALS IN CARCINOGENESIS: BIOCHEMISTRY AND METABOLISM.
Jennette KW
Dept. Chemistry, Dartmouth Coll., Hanover, NH, 03755
Environ Health Perspect; 40:233-252 1981

20. RECENT CONCEPTS OF INITIATION AND PROMOTION IN CARCINOGENESIS.
Becker FF
M. D. Anderson Hosp. and Tumor Inst., 6723 Bertner Ave., Houston, TX, 77030
Am J Pathol; 105(1):3-9 1981

21. ACTIVATED METABOLITES OF CARCINOGENIC HYDROCARBONS.
Harvey RG
Ben May Lab., Univ. Chicago, Chicago, IL, 60637
Acc Chem Res; 14(7):218-226 1981

22. RELATIONSHIP BETWEEN METAL TOXICITY TO SUBCELLULAR SYSTEMS AND THE CARCINOGENIC RESPONSE.
Squibb KS, Fowler BA
Lab. Pharmacology, Natl. Inst. Environmental Health Sciences, P.O. Box 12233, Research Triangle Park, NC, 27709
Environ Health Perspect; 40:181-188 1981

23. ENZYMES INVOLVED IN THE REPAIR OF DAMAGED DNA.
Grossman L
Dept. Biochemistry, Sch. Hygiene and Public Health, Johns Hopkins Univ., 615 N. Wolfe St., Baltimore, MD, 21205
Arch Biochem Biophys; 211(2):511-522 1981

24. METAL-INDUCED INFIDELITY OF DNA SYNTHESIS.
Zakour RA, Kunkel TA, Loeb LA
Joseph Gottstein Memorial Cancer Res. Lab., Dept. Pathol., Univ. Washington, Seattle, WA, 98195
Environ Health Perspect; 40:197-205 1981

25. CHROMOSOME ABERRATIONS AND THEIR RELEVANCE TO METAL CARCINOGENESIS.
Vainio H, Sorsa M
Dept. Industrial Hygiene and Toxicology, Inst. Occupational Health, Haartmaninkatu 1, SF-00290 Helsinki 29, Finland
Environ Health Perspect; 40:173-180 1981

MODIFICATION OF CARCINOGENESIS

26. METAL INTERACTIONS IN CARCINOGENESIS: ENHANCEMENT, INHIBITION.
Nordberg GF, Andersen O
Dept. Environmental Hygiene, Umea Univ., Umea, Sweden
Environ Health Perspect; 40:65-81 1981

27. EFFECT OF METALS ON MUTAGENESIS AND DNA REPAIR.
Rossman TG
Inst. Environmental Medicine, New York Univ. Sch. Medicine, 550 First Ave., New York, NY, 10016
Environ Health Perspect; 40:189-195 1981

METHODOLOGY IN CARCINOGENESIS RESEARCH

28. SISTER CHROMATID EXCHANGES: A REPORT OF THE GENE-TOX PROGRAM.
Latt SA, Allen J, Bloom SE, Carrano A, Falke E, Kram D, Schneider E, Schreck R, Tice R, Whitfield B, Wolff S
Harvard Medical Sch., Boston, MA, 02115
Mutat Res; 87(1):17-62 1981

29. EFFECTS OF METALS IN IN VITRO BIOASSAYS.
Sirover MA
Dept. Pharmacology, Temple Univ. Sch. Medicine, Philadelphia, PA, 19140
Environ Health Perspect; 40:163-172 1981

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Activation and Metabolism of Carcinogens

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service • National Institutes of Health • National Cancer Institute

HE 20. 3173/2:

METABOLIC ACTIVATION OF CARCINOGENS

1. CALCULATION OF REACTIVITY INDICES FOR BENZ(A)ANTHRACENE AND BENZO(A)PYRENE AND THEIR APPROXIMATIVE MODELS OF COMPLEX WITH ENZYME EPOXIDASE.

Miertus S, Majek P
Inst. Polymers, Slovak Acad. Sciences, 809 34 Bratislava, Czechoslovakia
Neoplasma; 28(4):441-446 1981

By theoretical methods of quantum mechanics an interaction between carcinogenic hydrocarbons - benz(a)anthracene, benz(a)pyrene - and various groups simulating an effect of enzyme oxidase has been studied. If accord is to be achieved with formation of epoxides of these compounds in vivo according to the bay region theory (ie, in A region) an interaction between the enzyme involving an electron-acceptor group and the bay region of hydrocarbon under simultaneous steric hindrance of the K region is necessary. Another possibility of obtaining the highest reactivity in the A region is to assume the formation of the radical cation as a first intermediate in the interaction with enzyme. (Author abstract) (9 Refs)

2. SLOWER STEP OF THE POLYCYCLIC AROMATIC HYDROCARBONS METABOLISM: KINETIC DATA FROM MICROSPECTROFLUOROMETRIC TECHNIQUES.

Salmon J-M, Thierry C, Serrou B, Viallet P
(c/o Serrou), Laboratoire d'Immunopharmacologie des Tumeurs, FRA-INSERM, B. P. 5054, 34033 Montpellier, France
Biomedicine; 34(4):102-107 1981

A microspectrofluorometer has been used for kinetic studies of the decrease of benzo(a)pyrene and benzo(k)fluoranthene fluorescence. This decrease is observed for single living cells: L cells and human peripheral blood monocytes, after their incubation with culture medium containing these compounds and washing the petri dish with fresh medium. The entire fluorescence spectra is recorded at given time intervals in order to watch at some eventual spectral modification. The fluorescence decrease is monoexponential and its parameters are computed with a program based on the least squares fit method. Such determination shows no difference between the calculated rate constants of metabolization for B(a)P and B(k)F and, as long as we consider L cells with a similar morphological shape, only statistical fluctuations of the rate constants of metabolism are observed. As compared, monocytes show faster kinetics of the decrease of the B(a)P intracellular fluorescence due to B(a)P metabolism, and also a more reached dispersion of the values of the rate constant than the one observed for L cells indicating some heterogeneity in the monocyte population of each donor. (Author abstract) (13 Refs)

3. ALPHA-HYDROXYLATION PATHWAY IN THE IN VITRO METABOLISM OF CARCINOGENIC NITROSAMINES: N-NITROSODIMETHYLAMINE AND N-NITROSO-N-METHYLANILINE.

Kroeger-Koepke MB, Koepke SR, McClusky GA, Magee PN, Michejda CJ
Chemical Carcinogenesis Program, Frederick Cancer Res. Center, Frederick, MD, 21701
Proc Natl Acad Sci USA; 78(10):6489-6493 1981

Evolution of 15N2-labeled molecular nitrogen was used to gauge the extent of alpha-hydroxylation during rat liver homogenate metabolism of doubly 15N-labeled N-nitrosodimethylamine (DMN) and N-nitrosomethylaniline (NMA). These measurements were correlated with the extent of total metabolism as measured by the disappearance of nitrosamines and by the formation of formaldehyde. The results indicate that approx 34% of DMN and 19% of NMA were metabolized by the alpha-hydroxylation pathway. Positive controls utilizing doubly 15-labeled N-nitroso-N-methylurea yielded 96% of labeled nitrogen. These results are in variance with previously published data which claimed that either less than 5% or about 100% of DMN is metabolized by the route in vitro. Formaldehyde formation was shown to be a poor measure of the extent of metabolism. Semicarbazide gave rise to both formaldehyde and nitrogen, which makes it an undesirable component of the in vitro metabolism mixtures, particularly when those two substances are being measured. (Author abstract) (32 Refs)

4. METABOLIC ALPHA-HYDROXYLATION OF N-NITROSOMORPHOLINE (MEETING ABSTRACT).

Hecht SS, Young R, Chen CB
American Health Foundation, Valhalla, NY, 10595
Toxicologist; 1(1):35 1981

N-Nitrosomorpholine (NM) is a potent carcinogen which induces liver tumors in rats and tumors of the trachea and nasal cavity in Syrian golden hamsters. 3,3,5,5-TetradeuteroNM is less carcinogenic and less mutagenic than NM, indicating that the metabolic activation of NM proceeds by hydroxylation of the 3 and 5 carbons (alpha carbons). However, metabolic alpha hydroxylation of NM has not been previously demonstrated. We incubated NM with rat liver microsomes and an NADPH generating system and demonstrated alpha hydroxylation by isolation of (2-hydroxyethoxy)acetaldehyde as its 2,4-dinitrophenylhydrazone (DNP) derivative. The rate of formation of (2-hydroxyethoxy)acetaldehyde in microsomal incubation mixtures can be assayed by reverse-phase high pressure liquid chromatography (HPLC) of its DNP. When rats were injected with NM, we did not detect (2-hydroxyethoxy)acetaldehyde in the urine, but we did isolate (2-hydroxyethoxy)acetic acid, which presumably resulted from further oxidation. Data will be presented on the deuterium isotope effect for alpha hydroxylation of NM and on the effects of mixed function oxidase inducers on alpha hydroxylation. (no Refs)

5. METABOLIC ALPHA-HYDROXYLATION OF N-NITROSOMORPHOLINE AND 3,3,5,5-TETRADEUTERO-N-NITROSOMORPHOLINE IN THE F344 RAT.

Hecht SS, Young R
Div. Chemical Carcinogenesis, American Health Foundation, Naylor Dana Inst. Disease Prevention, Valhalla, NY, 10595
Cancer Res; 41(12):5039-5043 1981

We studied the metabolism in the male F344 rat of N-nitrosomorpholine and of 3,3,5,5-tetradeutero-N-nitrosomorpholine; the latter is less carcinogenic and less mutagenic than is N-nitrosomorpholine. Alpha-Hydroxylation (3-or 5-hydroxylation) of N-nitrosomorpholine by liver microsomes and a reduced nicotinamide adenine dinucleotide phosphate-generating system produced (2-hydroxyethoxy)acetaldehyde, which was identified as its 2,4-dinitrophenylhydrazone derivative. When we administered N-nitrosomorpholine to rats ip, we did not detect (2-hydroxyethyl)a cetaldehyde in the urine, but we did identify (2-hydroxyethoxy)acetic acid (16% of the dose). We also identified N-nitroso(2-hydroxyethyl)glycine (33% of the dose) from beta-hydroxylation (2-or 6-hydroxylation), N-nitroso-diethanolamine (12%), and unchanged N-nitrosomorpholine (1.5%) in the urine. The deuterated analogs of the above metabolites were isolated from the urine of rats treated with 3,3,5,5-tetradeutero-N-nitrosomorpholine in yields as follows: (2-hydroxyethoxy)acetic acid (3.4%); N-nitroso(2-hydroxyethyl)glycine (37%); N-nitrosodiethanolamine (12%); N-nitrosomorpholine (0.4%). These data demonstrate that deuterium substitution in the alpha-positions of N-nitrosomorpholine caused a decrease in the extent of alpha-hydroxylation and indicate that alpha-hydroxylation is the mechanism of activation of N-nitrosomorpholine. (Author abstract) (31 Refs)

6. METABOLISM OF NITROSOACETOXYMETHYLMETHYLAMINE IN LIVER MICROSOMES.

Appel KE, Frank N, Wiessler M

Dept. Toxicology, Inst. Pharmacology, Obere Zahlbacher Str. 67, D-6500 Mainz, W. Germany

Biochem Pharmacol; 30(20):2767-2772 1981

The carcinogen nitrosoacetoxymethylmethylamine (NAMM) was incubated with mouse liver microsomes. The decomposition rate of NAMM and the formation of methanol were determined. After addition of an NADPH-regenerating system, formaldehyde formation resulting from metabolic degradation of the methyl group of NAMM was measured. The results suggest that NAMM is rapidly hydrolyzed by unspecific esterases to nitrosohydroxymethylmethylamine (NHMM). NHMM decomposes according to the activation mechanism of nitrosodimethylamine (NDMA). The formation of methanol proceeds with an even lower velocity. This indicates that intermediate breakdown products - probably NHMM or methyldiazohydroxide (MDH) - possess a distinct stability. Oxidative demethylation of NHMM or MDH was not detectable. The methanol formed is oxidized to formaldehyde by microsomal enzymes. (Author abstract) (31 Refs)

7. METABOLIC FATE OF N-METHYL-N-DODECYLNITROSAMINE IN THE RAT, IN RELATION TO ITS CARCINOGENICITY TO THE URINARY BLADDER.

Suzuki E, Mochizuki M, Okada M

Tokyo Biochemical Res. Inst., Takada 3-41-8, Toshima-ku, Tokyo 171, Japan

Gan; 72(5):713-716 1981

The metabolic fate of N-methyl-N-dodecylnitrosamine (MDN) was investigated in the rat, in order to elucidate a possible correlation between urinary metabolites and organotropic carcinogenicity to the urinary bladder of this N-nitrosamine. MDN was extensively metabolized in the rat, no unchanged MDN being found in the urine. The urinary metabolites identified were N-methyl-N-(3-carboxypropyl)nitrosamine (MCPN), N-methyl-N-(2-hydroxy-3-carboxypropyl)nitrosamine, N-methyl-N-(carboxymethyl)nitrosamine, and N-methyl-N-(2-oxopropyl)nitrosamine. Thus the metabolic pattern of MDN was essentially similar to that of N-methyl-N-(4-hydroxybutyl)nitrosamine, a potent bladder carcinogen, in the rat. A possible important role of MCPN in the induction of bladder tumors by MDN is discussed. (Author abstract) (21 Refs)

8. COMPREHENSIVE ANALYSIS OF URINARY METABOLITES OF N'-NITROSONORNICOTINE.

Hecht SS, Lin D, Chen CB

Div. Chemical Carcinogenesis, Naylor Dana Inst. Disease Prevention, American Health Foundation, Valhalla, NY, 10595

Carcinogenesis; 2(9):833-838 1981

Urinary N'-nitrosonornicotine (NNN) metabolites in male F-344 rats, male Syrian golden hamsters, and male A/J mice were quantified by high-pressure liquid chromatography. In F-344 rats injected with NNN (3-300 mg/kg), the main urinary products were hydroxy acid (37.2-53.3% of the administered dose), NNN-1-oxide (6.7%-10.7%), norcotinine (3.2-5.1%), keto acid (31.1%-12.8%), and NNN (3.3%-5.2%). Despite the differing organ specificity of NNN in the three species, urinary metabolites in mice and hamsters were qualitatively similar to those in rats. In each case, a marked capacity for 2'- and 5'-hydroxylation was observed. The in vivo metabolites resulting from 2'-hydroxylation of NNN by rat liver microsomes were myosmine and keto alcohol; both gave rise to keto acid as the major urinary metabolite. Lactol, the product of microsomal 5'-hydroxylation, gave hydroxy acid as its major urinary metabolite. The two major metabolites are probably reliable indicators of NNN alpha-hydroxylation in vivo. (19 Refs)

9. THE ORGAN CULTURE OF RAT ESOPHAGEAL MUCOSAL EPITHELIUM AND ITS RESPONSE TO N'-NITROSONORNICOTINE (MEETING ABSTRACT).

Reiss B, Hecht SS, Williams GM

Naylor Dana Institute for Disease Prevention, American Health Foundation, Valhalla, NY, 10595

In Vitro; 17(3):223 1981

Using techniques similar to those beneficial for the prolonged organ culture of rodent colon, we have maintained rodent esophagus for up to 35 days. During this interval, the normal architecture and histology of the mucosal epithelium were preserved, and normal cell proliferation and keratinization were retained. Kinetic studies of cells labelled during DNA synthesis demonstrated a continuation of epithelial cell maturation and migration for at least 4 wk. Exposure to the model esophageal carcinogen, N'-nitrosonornicotine (NNN; 10(-2) M) for 48 hr in culture suppressed DNA synthesis of conventional rat esophageal mucosa at 2 days; higher incorporation than controls occurred at 1, 2 and 3 wk. Exposure to 14C-NNN for 48 hr resulted in the formation of 4-oxo-4-(3-pyridyl)butyric acid from 2'-hydroxylation and 4-hydroxy-4-(3-pyridyl)butyric acid from 5'-hydroxylation of NNN. The levels of these metabolites indicated that, unlike the hepatic metabolism of NNN, the extent of 2'-hydroxylation in the esophagus exceeds that of 5'-hydroxylation. These results may provide the metabolic basis for the organo-selectivity of NNN. Fragments of organ-cultured esophagus implanted into mammary fat pads of syngeneic animals have been maintained for up to 6 mo. Fragments exposed to NNN for 48 hr and then implanted developed a hyperplastic mucosal epithelium after 2 mo in the host. This potentially preneoplastic change was not observed in controls. (1 Ref)

10. THE EFFECT OF THE PANCREATIC CARCINOGEN N-NITROSO-2-METHOXY-2,6,-DIMETHYL-MORPHOLINE ON ENDOCRINE AND EXOCRINE PANCREAS OF SYRIAN HAMSTERS (MEETING ABSTRACT).

Pour PM
The Eppley Institute for Research in Cancer, Omaha, NE
Eighth European Congress of Pathology, August 30-September 4, 1981, Helsinki, Finland. The Congress 92 pp., 1981.

All nitrosamines with a pancreatic carcinogenic effect of Syrian hamsters have a common metabolite, N-nitroso(-2-hydroxypropyl) (2-oxopropyl)amine (HPOP). As the cyclic structure of this metabolite, resembling the pyranose form of the hexose-sugars and the sugar moeity of the Streptozocin (SZ), may be responsible for its affinity for the pancreas, we studied the effect of N-nitroso-2-methoxy-2,6-dimethyl nitrosomorpholine (MeNDNM), a fixed cyclic form of HPOP. We found that a single high dose of this compound exhibited, compared to the effect of SZ, selective necrosis of the B-cells of pancreatic islets within 3 days. In surviving hamsters the islets showed signs of regeneration, which was completed within 60-72 hr. Some 40 wk later, however, and in contrast to the effect of SZ, almost all treated hamsters developed pancreatic ductular and mixed ductular-insular tumors. On the other hand, weekly application of MeNDNM in subdiabetogenic induced equivalent tumors, but did not appear to affect islet cells. These results point to the mutual response of the endocrine and exocrine pancreas to this compound, thus indicating the importance of the carcinogen's cyclic structure. Possible mechanisms involved in pancreatotropic effects of this class of chemical carcinogens will be discussed. (no Refs)

11. RELATIONSHIP OF RAT URINARY METABOLITES OF N-NITROSOMETHYL-N-ALKYLAMINE TO BLADDER CARCINOGENESIS.

Singer GM, Lijinsky W, Buettner L, McClusky GA
Chemical Carcinogenesis Program, Frederick Cancer Res. Center, Frederick, MD, 21701
Cancer Res; 41(12):4942-4946 1981

Nitrosomethylalkylamines with chain lengths from C4 (n-butyl-) to C14 (n-tetradecyl-) were each administered to three rats at doses equimolar with 12 mg of the butyl compound. All of the compounds administered to rats at this dose, twice a wk for 30 wk, induced tumors in 100% of the animals. Some of the compounds with even-numbered alkyl chains induced bladder tumors, and a connection was sought with the metabolites of these excreted in urine. The pooled 24-hr urine was extracted with ethyl acetate before and after acidification to provide a neutral fraction and a fraction containing nitrosamino acids. The fraction containing the acids was analyzed by capillary gas chromatography and by gas chromatography-mass spectrometry after esterification with diazomethane; the neutral fraction was analyzed similarly. The principal metabolite of the nitrosamines with odd-numbered chains was found in the acidic fraction and was identified as nitrosomethyl-2-carboxyethylamine. There were several acids in the mixtures derived from the nitrosamines with even-numbered chains, nitrososarcosine and nitrosomethyl-3-carboxypropylamine being the major components. There was no trend in the yields of the nitrosamino acids that could be correlated with the differences in carcinogenic potency between the nitrosamines; the max yield of acids was more than 30% (from the tetradecyl compound). The principal component of the neutral fraction (+-1% of the nitrosomethylalkylamine administered) was nitrosomethyl-2-oxopropylamine. The yield of this compound increased with increasing length of the even-numbered chain nitrosamines. (Author abstract) (14 Refs)

12. THE CHEMISTRY OF ACTIVATED INTERMEDIATES OF N-NITROSO COMPOUNDS CONTAINING THE 2-OXOPROPYL GROUP (MEETING ABSTRACT).

Nagel D, Wallcave L, Mirvish S, Smith J
Eppley Institute for Research in Cancer, University of Nebraska Medical Center, Omaha, NE, 68105
Newsletter Natl Pancreas Cancer Project; VI(2):43 1981

To date all N-nitrosamines which contain or are metabolized to nitrosamines containing a 2-oxopropyl group have been shown to induce pancreatic adenocarinoma in the Syrian hamster. Within this series of nitrosamines bis(2-oxopropyl)nitrosamine (BOP) is the most specific for the hamster pancreas while methyl-2-oxopropyl-nitrosamine (MOP) is the most potent (MOP induces tumors in the hamster pancreas and other organs with a single dose of 2.5 mg/kg). In vivo alkylation studies have shown that BOP predominantly methylates pancreatic DNA while liver DNA is both methylated and alkylated with a longer alkyl group of unknown nature (perhaps a 2-oxopropyl group). Two mechanisms of activation of BOP appear plausible. (1) BOP is metabolized to MOP which in turn is alpha hydroxylated yielding either a methylating on 2-oxopropylating species which can react with cellular macromolecules including DNA, producing methylated or oxopropylated adducts. 2) Alternatively BOP is alpha hydroxylated and decomposes by two different routes. The classical decomposition pathway would lead to a 2-oxopropylating species while a second competing pathway would lead to a methylating species. To test these hypotheses we have prepared ethyl-N-nitroso-2-oxopropylcarbamate (OPC) and the two alpha acetoxy derivatives of MOP [N-acetoxymethyl-N-2-oxopropylnitrosamine (AMOP) and N-methyl-N-(1-acetoxy-2-oxopropyl)amine (MAOP)] and studied their soln chemistry and reactions with selected nucleophiles. OPC reacts with 3,4-dichlorothiophenol producing both methylated and oxopropylated thioethers supporting the second hypothesis while the extreme reactivity of MAOP in solvolysis studies in comparison to alpha-acetoxydimethylnitrosamine tends to support the first hypothesis. (no Refs)

13. THE FORMATION OF N-NITROSOMETHYL(2-OXOPROPYL)AMINE FROM N-NITROSOBIS(2-OXOPROPYL)AMINE IN VIVO.

Lawson TA, Helgeson AS, Grandjean CJ, Wallcave L, Nagel D
Eppley Inst. Res. Cancer 0613, Univ. Nebraska Medical Center, 42nd and Dewey Ave., Omaha, NB, 68105
Carcinogenesis; 2(9):845-849 1981

Tissue concentrations of N-nitrosobis(2-oxopropyl)amine (BOP) and its metabolites in male Syrian golden hamsters given a single dose of BOP (10 mg/kg, sc) were analyzed by gas chromaography. BOP concentrations were higher in the pancreas than in the liver or salivary glands. N-nitrosomethyl(2-oxopropyl)amine (MOP) was present in higher concentrations in the pancreas than in the liver, and N-nitroso(2-hydroxypropyl)(2-oxopropyl)amine also was preferentially taken up by the pancreas. The results strongly suggested that MOP is a proximate carcinogenic metabolite of BOP. (15 Refs)

14. PEROXIDASE ACTIVATION OF N-OH-AAF BY RAT MAMMARY GLAND PARENCHYMAL CELLS (MEETING ABSTRACT).

Wong PK, Hampton MJ, Floyd RA
Oklahoma Medical Research Foundation, Oklahoma City, OK
International Conference on Prostaglandins and Cancer, August 30-September 2, 1981, Washington, DC. Lombardi Cancer Center 75 pp., 1981.

Rat mammary gland parenchymal cells activate N-hydroxy-2-acetylaminofluorene (N-OH-AAF) to 2-nitrosofluorene (NOF) and N-acetoxy-2-acetylaminofluorene (N-OAC-AAF) via a nitroxyl free radical form of the carcinogen. Prostaglandin synthetase has a peroxidase activity and hence we have examined parenchymal cells to determine if the activation of N-OH-AAF in the cells occurs by this route. Freshly isolated cells activate N-OH-AAF to NOF as detected by high pressure liquid chromatography (HPLC). Cells frozen at-60C are more active. N-OH-AAF activation appears to be peroxidative since ascorbate and p-aminophenol completely inhibit NOF formation. Neither the acyl-transferase nor deacylase route occurs to any appreciable extent in the cells. Exogenously added arachidonate enhances N-OH-AAF activation and the inhibitor 5,8,11,14-eicosatetraynoic acid (ETYA) considerably decreased N-OH-AAF activation while indomethacin or aspirin were not effective. Ram seminal vesicle microsomes activate N-OH-AAF apparently by prostaglandin synthetase. Our work indicates that N-OH-AAF was activated by lipoxygenase pathway in these cells. The 12L-hydroperoxy-5,8,10,14-icosatetraenoic acid (12-HPETE) generated through endogenous or exogenous arachidonate sources probably is the hydroperoxide substrate for the peroxidase. Platelets which are rich in lipoxygenase also activate N-OH-AAF. Since 12-HPETE is one of the three hydroperoxides found in animal kingdom, the peroxidase activation may have significant importance in mammary gland carcinogenesis. (no Refs)

15. METABOLISM AND DISPOSITION OF TRIS BP IN THE RAT (MEETING ABSTRACT).

Matthews HB, Nomeir AA
National Institute of Environmental Health Science and National, Toxicology Program Research Triangle Park, NC, 27709
Toxicologist; 1(1):35 1981

The flame retardant chemical tris (2,3-dibromopropyl)phosphate (Tris BP), has been shown to be carcinogenic in laboratory animals. In an effort to provide additional data on the disposition of Tris BP in laboratory animals the oral and dermal absorption, tissue distribution, metabolism and excretion of 14C-labeled Tris BP have been studied in the rat. The results of these studies indicate that Tris BP is readily absorbed from the gastrointestinal tract and absorbed at an appreciable rate from the skin. Following absorption Tris BP is distributed to all the major tissues, but Tris BP derived radioactivity is most concentrated in liver, blood and kidney. Tris BP is readily metabolized and excreted in the form of several polar metabolites in urine and feces and as CO2 in exhaled air. Six metabolites of Tris BP have been isolated and identified from urine and bile. Excretion of unmetabolized Tris BP is negligible. In vitro studies of Tris BP metabolism have demonstrated that enzymes in liver degrade the parent chemical to the same polar metabolites which were isolated and identified from urine and bile. The enzymes responsible for Tris BP metabolism are concentrated in microsomal and soluble portions of liver homogenates and require NADPH and glutathione, respectively, as cofactors for enzyme activity. (no Refs)

OTHER METABOLISM OF CARCINOGENS

16. EFFECTS OF CARCINOGENS, MUTAGENS, AND TERATOGENS ON NON-HUMAN SPECIES-AQUATIC ANIMALS (MEETING ABSTRACT).

Couch JA, Schoor WP
United States Environmental Protection Agency, Gulf Breeze, FL
Second Annual NCI/EPA/NIOSH Collaborative Workshop: Progress on Joint Environmental and Occupational Cancer Studies, September 9-11, 1981, Rockville, Maryland. National Cancer Institute 33 pp., 1981.

Aquatic systems and organisms are under both laboratory and field study in order to develop indicator, screening, and modeling capabilities for detection and evaluation of risks of carcinogens, mutagens, and teratogens. In the third yr of the program, several advances were made in the development of minnow (liver lesions via benzidine and aflatoxin exposures), rainbow trout (liver tumors via benzo(a)pyrene (B(a)P) exposures), and freshwater catfish (papillomatous-like lesions via chlorinated effluent exposures). A novel approach has shown that tiger salamanders may be good biochemical and histologic indicators of the presence of certain carcinogens (polycyclic aromatic hydrocarbons-PAH's). The skin and liver tissues of the salamanders revealed induced enzyme activity following exposure to the PAH, perylene. Considerable field monitoring work on mollusks and carcinogenic PAH's along the coast of Oregon has revealed a positive correlation between prevalence of cellular proliferation disorders in shellfish and higher concentrations of certain PAH's in natural water. Emphasis in biochemistry for the last yr has been directed mostly toward the elucidation of the metabolisms of the mixed-function oxidases in marine organisms. From continuing work on the mullet (Mugil cephalus), we have found that benzo(a)pyrene is converted mainly to 3-hydroxybenzo(a)pyrene, 9-hydroxybenzo(a)pyrene and 4, 5-,7,8-,9,10-dihydroxydiols of B(a)P, in in vitro systems containing liver microsomes from Aroclor 1254-treated mullet. Other metabolites such as diones of B(a)P and probably tri- and tetraols have also been produced. We have also developed a procedure for the epoxide hydrolase enzyme system in order to determine the role of this enzyme on the metabolism of the polyaromatic hydrocarbons. These studies continue to reveal that fish have similar metabolic pathways to mammals for disposition of certain carcinogens. (no Refs)

17. URINARY METABOLITES OF N-NITROSODIPROPYLAMINE, N-NITROSO-2-HYDROXYPROPYLPROPYLAMINE AND N-NITROSO-2-OXOPROPYLPROPYLAMINE IN THE RAT.

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Carcinogenesis; 2(9):859-862 1981

Male Sprague-Dawley rats in groups of two animals each were inoculated ip with N-nitrosodipropylamine (NDPA: 77 mg/kg), N-nitroso-2-hydroxypropylpropylamine (NHPPA: 86 mg/kg), or N-nitroso-2-oxopropylpropylamine (NOPPA: 85 mg/kg). In each case, the major urinary metabolite was the beta-glucuronide of NHPPA. Exhaustive hydrolysis of 24-hr urine samples with beta-glucuronidase yielded conjugated NHPPA in amounts corresponding to 5%, 80%, and 50% of the administered doses of NDPA, NHPPA, and NOPPA, respectively. Levels of unchanged nitrosamines and their metabolites (NHPPA for administered NDPA or NOPPA were generally low: less than 2% of the administered dose). N-nitrosomethylpropylamine and N-nitrosodimethylamine were not detected in any urine samples. (22 Refs)

18. ENTEROHEPATIC FATE OF AFLATOXIN B1 (MEETING ABSTRACT).

Wong JJ, Kayashima L, Hsieh PH
Department of Environmental Toxicology, University of California, Davis, CA, 95616

Toxicologist; 1(1):33 1981

Previous metabolic research on the potent food-borne carcinogen, aflatoxin B1 (AFB1) has primarily focused upon the liver and only speculated upon its interrelationship with the gastrointestinal tract in AFB1 disposition and toxicity. Using in situ metabolism techniques, male Sprague-Dawley rats received intestinal doses of 14C-AFB1 equivalent to that calculated for 24 hr dietary exposure to 1ppm AFB1. Curve-fit estimates of AFB1 absorption indicates that the total hepatic exposure to AFB1 would equal approx 5 ug or 27% of dose within 24 hr. Intraportal injection of less than 4 ug of AFB1 indicates that excretion in the bile begins within 10 min. Estimates indicate that within 24 hr approx 64% of dose would be excreted in the bile. High pressure liquid chromatography and thin layer chromatography analysis of the bile failed to detect AFB1 or any of its known metabolites. Preliminary Ames mutagen tests have not detected any bile-borne mutagenic activity. Venous blood sampled from the inferior vena cava revealed a concentration of less than 1.0% of dose/ml blood. Approx 40% of this amount was bound to blood proteins, 30% associated with aqueous phase, and no 'free' AFB1 detected. Re-injection of bile into the small intestine did not result in detectable reabsorption. Evidence indicates that during chronic dietary exposure to AFB1, the liver is capable of substantial first-pass extraction and efficient biliary elimination of AFB1 metabolites. Biliary-borne metabolites appear to represent detoxification products and not subject to enterohepatic recirculation. (no Refs)

19. THE METABOLISM AND EXCRETION OF STYRENE OXIDE-GLUTATHIONE CONJUGATES IN THE RAT AND BY ISOLATED PERFUSED LIVER, LUNG AND KIDNEY PERFUSIONS.

Steele JW, Yagen B, Hernandez O, Cox RH, Smith BR, Bend JR
(c/o Bend) Lab. Pharmacology, NIEHS/NIH, P.O. Box 12233, Research Triangle Park, NC, 27709

J Pharmacol Exp Ther; 219(1):35-41 1981

The metabolism and excretion of styrene oxide (SO)-glutathione conjugates (SO-GSH) were studied in the intact rat by isolated perfusion techniques in rat lung, liver and kidney. Styrene, or its metabolite SO, constitutes a potential biohazard, since the latter is a known mutagen. The experiments demonstrated that the rat is capable of rapid conversion of SO-GSH to various derivative metabolites, and of rapid excretion of all SO thioether conjugates. (22 Refs)

20. MOLECULAR MECHANISMS INVOLVED IN THE BLADDER TOXICITY OF SODIUM ORTHOPHENYLPHENOL (SOPP) (MEETING ABSTRACT).

Reitz RH, Fox TR, Quast JF, Hermann EA, Watanabe PG
Dow Chemical, Midland, MI

International Symposium on Health Effects of Tumor Promotion, October 12-15, 1981, Cincinnati, Ohio US Environmental Protection Agency and the American College of Toxicology; 1981

SOPP has been reported to increase urinary tumors in rats. However, OPP (free base) and SOPP failed to produce mutations in 5 strains of Salmonella typhimurium and SOPP did not induce unscheduled DNA synthesis in rat hepatocytes. DNA alkylation was not detected after gavage with 500 mg/kg of OPP or SOPP. These studies suggest little or no genotoxicity for these materials. Animals consuming diets with 2 percent OPP or SOPP were sacrificed after 3, 7, 14, 30, and 90 days. Progressive hyperplasia of bladder epithelium was noted in the SOPP group, but was absent in the OPP group. Focal kidney lesions were observed in the OPP group, but were largely absent in the SOPP group. The metabolism of both OPP and SOPP was dose dependent. Below 150 mg/kg, 90-97 percent of the urinary metabolites were identified as sulfate and glucuronide conjugates, with 3-6 percent oxidation products apparently derived from microsomal (MFO) pathways. Following 500 mg/kg (gavage) or dietary administration (2 percent) or OPP and SOPP, 20-30 percent of the urinary metabolites were oxidation products. Thus the production of reactive MFO metabolites may be correlated with the bladder toxicity observed in rats consuming diets containing high levels of SOPP but not observed after low levels of SOPP. The lack of genotoxicity of OPP and SOPP coupled with the dose dependent production of an oxidative metabolite suggests that the toxicity and carcinogenicity may be manifest only at high metabolically saturating doses. (1 Ref)

MODIFICATION OF CARCINOGEN METABOLISM

21. SPECIFICITY IN THE ACTIVATION AND INHIBITION BY FLAVONOIDS OF BENZO[A]PYRENE HYDROXYLATION BY CYTOCHROME P-450 ISOZYMES FROM RABBIT LIVER MICROSOMES.

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J Biol Chem; 256(21):10897-10901 1981

The effect of flavone and 7,8-benzoflavone on the metabolism of benzo[a]pyrene to fluorescent phenols by five cytochrome P-450 isozymes obtained from rabbit liver microsomes was determined. Benzo[a]pyrene metabolism was stimulated more than five-fold by the addition of 600 uM flavone to a reconstituted monooxygenase system consisting of NADPH, cytochrome P-450 reductase, dilauroylphosphatidylcholine, and cytochrome P-450LM3c or cytochrome P-450LM4. In contrast, an inhibitory effect of flavone on benzo[a]pyrene metabolism was observed when cytochrome P-450LM2, cytochrome P-450LM3b, or cytochrome P-450LM6 was used in the reconstituted system. 7,8-Benzoflavone (50-100 uM) stimulated benzo[a]pyrene metabolism by the reconstituted monooxygenase system about 10-fold when cytochrome P-450LM3c was used, but benzo[a]pyrene hydroxylation was strongly inhibited when 7,8-benzoflavone was added to the cytochrome P-450LM6-dependent system. Smaller effects of 7,8-benzoflavone were observed on the metabolism of benzo[a]pyrene by the cytochrome P-450LM2-, cytochrome P-450LM3b-, and cytochrome P-450LM4-dependent monooxygenase systems. These results demonstrate that the activating and inhibiting effects of flavone and 7,8-benzoflavone on benzo[a]pyrene metabolism depend on the type of cytochrome P-450 used in the reconstituted monooxygenase system. (Author abstract) (44 Refs)

22. METABOLISM OF BENZO(A)PYRENE BY BRAIN MICROSOMES OF FETAL AND ADULT RATS AND MICE. INDUCTION BY 5,6-BENZOFLAVONE, COMPARISON WITH LIVER AND LUNG MICROSOMAL ACTIVITIES.

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Carcinogenesis; 2(9):919-926 1981

Pregnant C57Bl/6 mice and WAG rats were injected ip with 5,6-benzoflavone (BF). On day 19 of gestation the animals were sacrificed, and fetal and maternal brain, lung, and liver microsomes were incubated with benzo(a)pyrene (BP). Liver microsomes of pregnant female mice were only slightly inducible compared with 10x and 4x control level induction of brain and lung microsomes. A 40x, 2x, and 16x control induction by BF was observed for fetal microsomes from the liver, brain, and lung, respectively. In rats, BP metabolism by brain microsomes was greater than that by lung microsomes. (44 Refs)

23. THE METABOLISM OF BENZO(A)PYRENE IN TRANSFORMABLE AND NONTRANSFORMABLE C3H MOUSE FIBROBLAST CELL LINES.

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Diss Abstr Int [B]; 42(3):913-B 1981

Incubation of benzo(a)pyrene (BaP) with intact C3H/10T1/2 cells for 48 hr resulted in the conversion of this carcinogen to organic-soluble derivatives, which cochromatographed with benzo(a)pyrene-7,8-dihydrodiol, benzo(a)pyrene-9,10-dihydrodiol, and 3-and 9-hydroxybenzo(a)pyrene, and to water-soluble derivatives. The metabolic activation of BaP was studied by testing a comprehensive series of 9 BaP metabolites for their ability to transform C3H/10T1/2 cells. Of all the derivatives examined, only (+/-) benzo(a)pyrene-7,8-dihydrodiol was as active as the parent hydrocarbon in the production of oncogenic transformation. In addition, the major DNA-binding species produced in BaP-treated C3H/10T1/2 cells was identified as benzo(a)pyrene-7,8-dihydrodiol-9,10-epoxide. These results strongly support current proposals that benzo(a)pyrene-7,8-dihydrodiol and benzo(a)pyrene-7,8-dihydrodiol-9,10-epoxide are the proximal and ultimate carcinogenic forms of BaP. The basis for cellular susceptibility to oncogenic transformation was investigated by comparing the metabolism of BaP by CVP3SC6 (CVP) cells, which are not responsive to BaP-induced transformation, and by C3H/10T1/2 cells. Although CVP cell microsomes were not as active as C3H/10T1/2 cell microsomes in the metabolism of BaP, its metabolism by intact CVP and C3H/10T1/2 cells was quantitatively and qualitatively very similar. CVP cells could be transformed by BaP treatment plus exposure to the tumor promoter, 12-O-tetradecanoylphorbol-13-acetate (TPA). CVP cells treated with BaP plus TPA exhibited both morphological alterations and a loss of anchorage dependence. These studies emphasize that not only metabolic activation leading to DNA adduct formation and mutagenesis, but also the ability to express carcinogen-induced damage play an important role in determining cellular susceptibility to carcinogenesis. (no Refs)

24. METABOLISM OF BENZO[A]PYRENE IN RAT PROSTATE GLANDS FOLLOWING 2,3,7,8-TETRACHORODIBENZO-P-DIOXIN EXPOSURE.

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Carcinogenesis; 2(9):823-831 1981

Benzo(a)pyrene (BP) metabolism was studied in the prostate glands of adult Sprague-Dawley rats treated with the potent monooxygenase inducer 2,3,7,8-tetrachorodibenzo-p-dioxin (TCDD: 2.5, 5, or 10 ug/kg, po). TCDD not only caused selective induction of prostatic aryl hydrocarbon hydroxylase (AHH) and cytochrome P-446, but also resulted in a significant increase in organic-soluble BP metabolites over aqueous conjugated metabolites. High-pressure liquid chromatography analysis showed that formation rates of phenols, quinones, and dihydrodiols in TCDD-induced prostate glands were, respectively, 290, 192, and 38 times higher than in noninduced glands. The rate of 7,8-diol formation was 1.5 times that of 4,5-diol and 3 times that of 9,10 diol. TCDD-induced increases in BP metabolites were dose dependent, and they coincided with the magnitude of AHH induction The possibility that increased 7,8-diol synthesis could lead to increased synthesis of the ultimate BP carcinogen and prostate tumor induction is discussed. (30 Refs)

25. COMPARISON OF THE PROMOTING ACTIVITY OF PRISTANE AND N-ALKANES IN SKIN CARCINOGENESIS WITH THEIR PHYSICAL EFFECTS ON MICELLAR MODELS OF BIOLOGICAL MEMBRANES.

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Biochim Biophys Acta; 648(1):107-112 1981

In 1976 we assayed pristane (2,6,10,14-tetramethylpentadecane) in a model interfacial system that has given excellent correlation with cocarcinogenic activity among n-alkanes, as tested in cycloalkane diluents. It was predicted that this branched-chain derivative of the diterpenes would have higher activity than n-$C_{18}H_{38}$, one of the most cocarcinogenic of the n-alkanes in such diluents. pristane was compared with n-$C_{18}H_{38}$ and two other n-alkanes for their promoting activities in cyclohexane for C3H male mice after a single application of 7,12-dimethylbenz[a]anthracene. The branched-chain alkane proved to be more active. Twenty percent n-tetracosane in cyclohexane was inactive, which correlated with its effects in this diluent in the physical assay system. The promoting activity of 75% n-octane in cyclohexane, predicted by the physical assay, was confirmed by tests on mice. The combined by-products of the synthesis of tetracosane, including C12 alkanes and alkenes, C19 and C20 alkylbenzenes, and C24 alkenes, proved to be a very active promoter. However, a mixture in cyclohexane of purified tetracosane with this composite of potential impurities was inactive. From the alkanes' behavior in physical systems involving various membrane phospholipids and steroids, it is hypothesized that the primary step in their biological activity is a chain-chain interaction with membrane lipids that alters the properties of liquid-crystalline phases at aqueous interfaces. Resulting changes in the microfluidity of the lipid phase and the lateral mobility of critical hormone receptors and enzyme systems, such as the nucleotidyl cyclases, would perturb control systems that maintain the normal behavior of the initiated cell. Thus, its progression to a proliferating neoplasm may be favored. (Author abstract) (13 Refs)

26. MODIFICATION OF BENZO(A)PYRENE-INDUCED CELLULAR TRANSFORMATION OF C3H/10T1/2 CELLS BY DEXAMETHASONE AND PREGNENOLONE-16ALPHA-CARBONITRILE (MEETING ABSTRACT).

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In Vitro; 17(3):223 1981

Most chemical carcinogens exist in the environment in an unreactive form and require metabolic activation to exert their biological activity. Manipulation of the microsomal enzymes has been proposed as a mechanism for controlling carcinogenesis. In this study two compounds, dexamethasone (DEX) and pregnenolone-16alpha-carbonitrile (PCN), are potent inducers of microsomal enzymes in vivo. Since these enzymes are responsible for the metabolism of carcinogens, the effects of these compounds were studied to determine whether increased enzyme activity was correlated with cellular transformation. Both DEX and PCN were found to induce AHH activity in the C3H/10T1/2 cells by about 2 fold and both compounds increased the rate of metabolism of benzo(a)pyrene to water-soluble products. The steroids however had opposite effects on transformation. DEX inhibited cellular transformation by about 65% at 23 uM concentration. PCN, however, was found to increase the frequency of transformation by more than 100%. Therefore, enhanced AHH activity and metabolism does not necessarily lead to enhanced transformation since other pathways of metabolism, carcinogen detoxification, or repair processes may be involved. (no Refs)

27. EFFECTS OF CADMIUM IN VITRO ON BENZO(A)PYRENE METABOLISM BY RAT TESTICULAR AND HEPATIC MICROSOMES (MEETING ABSTRACT).

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Toxicologist; 1(1):121 1981

Cadmium is known to have toxic effects on the testes as well as to inhibit microsomal mixed function oxidase activity in a variety of tissues. Studies were carried out to compare the actions of cadmium in vitro on testicular and hepatic metabolism of benzo(a)pyrene (BP), a compound which requires metabolic activation for its mutagenic and carcinogenic effects. Testicular and hepatic microsomes were obtained from normal male rats and incubated with BP in the presence of saturating concentrations of NADPH and varying (2 x 10(-4) M -5 x 10(-6) M) concentrations of cadmium. In liver microsomes, cadmium produced a dose-dependent decrease in the production of fluorescent metabolites (phenols). By contrast, in testicular microsomes, the lower concentrations of cadmium (2.5 and 5 x 10(-5) M) enhanced the formation of phenols whereas higher levels (greater than 1 x 10(-4) M) decreased the production of fluorescent metabolites. To determine if the changes in testicular production of phenolic metabolites might be related to alterations in competing metabolic pathways, the effects of cadmium on the activity of epoxide hydrase, an enzyme required for the production of dihydrodiol metabolites, were investigated. Cadmium produced a dose-dependent inhibition of epoxide hydrase activity in both testicular and hepatic microsomes. The effects in testes were greater than those in liver. Preliminary analysis of BP metabolites by high performance liquid chromatography further indicates that cadmium affects the production of both phenols and dihydrodiols by testicular and hepatic microsomes. The results demonstrate that cadmium alters the routes of metabolism of BP in the testes and may therefore, influence its toxicity. (no Refs)

28. COMPARISON OF HEPATIC CARCINOGEN INITIATION-PROMOTION SYSTEM (MEETING ABSTRACT).

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Toxicologist; 1(1):154 1981

A number of model systems have been designed to study the initiating and promoting phases of neoplastic development in rat liver. The purpose of these experiments was to determine if the promoting protocols alone altered liver biochemistry. Four protocols, which use the same initiator, diethylnitrosamine (DEN), but different promotional regimens, were investigated. The biochemical parameters evaluated were hepatic microsomal benzphetamine-N-demethylase (BPND), epoxide hydratase (EH), cytosolic DT-diaphorase, serum glutamic pyruvic transaminase (GPT) and serum gamma glutamyl transpeptidase (GGT) activities. The effect of initiation in these protocols was also evaluated to ascertain if DEN caused changes in liver biochemistry and if these changes were related to preneoplastic lesions. All 4 promoting regimes depressed BPND (20-50% of control) and all except one increased EH and DTD (3-fold). SGGT was elevated by all protocols (10x) but SGPT was only slightly changed. The combination of DEN initiation with promotion increased hepatic GGT positive foci (identified histochemically) but did not alter the biochemical parameters studied. We conclude that measurement of these enzymes is of no value for predicting neoplastic change. However, the data show that liver biochemistry, especially with respect to drug metabolism, is extensively altered by the promotional regimes. Consequently, study of promoter-induced changes in drug metabolizing enzymes may lead to a better understanding of biochemical events during promotion in hepatocarcinogenesis. (4 Refs)

29. THE EFFECT OF PROMOTERS ON BLADDER CANCER INCIDENCE IN EXPERIMENTAL ANIMAL MODELS (MEETING ABSTRACT).

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International Symposium on Health Effects of Tumor Promotion, October 12-15, 1981, Cincinnati, Ohio US Environmental Protection Agency and the American College of Toxicology; 1981

Multistage models of carcinogenesis have been proposed to account for the observed patterns of tumor development in the skin, liver, lung, bladder and other organs. Such models involve initiation of neoplastic change in a few cells by a threshold dose of carcinogen, followed by conversion of these latent tumor cells into an autonomous cancer by further doses of the same and/or other carcinogens, and/or non-carcinogenic promoting agents. In the rat urinary bladder neoplastic change can be initiated by a few wk treatment with low doses of N-butyl-N-(4-hydroxybutyl)nitrosamine (BBN) or N-(4-(5-nitro-2-furyl)-2-thiazolyl)formamide (FANFT) or by a single, low dose, intravesicular instillation of N-methyl-N-nitrosourea (MNU). Very few of the animals treated in such a way will develop bladder cancer in their natural life span unless, in addition, they are exposed subsequently to some further regime which will promote tumor growth from the initiated tumor cells. Many different factors will promote tumor growth in the initiated rat bladder including further low doses of complete bladder carcinogens, some dietary factors such as metabolites of tryptophan or deficiency of vitamin A, the food additives saccharin and cyclamate, and some alkylating agents such as cyclophosphamide and methylmethanesulphonate. Although promoters do not necessarily have all the attributes of complete carcinogens, and may not be mutagenic, by accelerating the process of tumor development and thus lowering the age-related cancer incidence in any particular population they may be of prime importance in regulating overall cancer statistics. (no Refs)

30. PROTECTIVE EFFECT OF ETHANOL ON THE DEVELOPMENT OF PANCREATIC CANCER (MEETING ABSTRACT).

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No affiliation given
Newsletter Natl Pancreas Cancer Project; VI(2):61 1981

We examined the effects of chronic ethanol ingestion on pancreatic function and the appearance of pancreatic neoplasms in hamsters. Three groups of animals were fed standard laboratory chow and water ad lib. Group 1 received no other treatment. Group 2 received a single injection of N-nitrosobis(2-oxopropyl)amine (BOP) (20 mg/kg sc), a dose known to produce pancreatic carcinomas within 28 wk. Group 3 had ethanol added to the drinking water (25% wt/vol) for the duration of the study, and received the same dose of BOP 2 wk after starting the ethanol treatment. After 24 wk, pancreatic juice was collected following secretin and cholecystokinin stimulation, and the pancreases were examined histologically by one of us who had no knowledge of the treatment regimen. The presence of ductal proliferation (Proliferative Index, PI) and neoplastic lesions (adenoma, carcinoma in situ, carcinoma) was recorded. The blood ethanol concentration was 130 +/-8 mg% in Group 3 animals. Chronic ethanol ingestion was associated with significantly less preneoplastic ductal proliferation and fewer neoplastic pancreatic lesions. The explanation for this observation is uncertain, but it may be related to ethanol's known ability to alter the metabolism of pancreatic secretory cells. Thus the carcinogen may have been metabolized differently in these animals. (no Refs)

31. EFFECT OF INHIBITORS OF TUMORIGENESIS ON THE FORMATION OF O6-METHYLGUANINE IN THE COLON OF 1,2-DIMETHYLHYDRAZINE-TREATED RATS.

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Cancer Res; 41(12):4938-4941 1981

The level of O6-methylguanine (O6MeGua) in the colonic DNA of rats treated with 1,2-dimethylhydrazine was determined. The effect of various tumorigenesis inhibitors on the formation of this modified base was also studied. Rats were given a single sc injection of 1,2-[14C]dimethylhydrazine. Six hours later, they were killed, and colonic DNA was extracted and analyzed by high-pressure liquid chromatography. The inhibitors tested were disulfiram (DSF), pyrazole, sodium selenite, butylated hydroxyanisole, butylated hydroxytoluene, potassium ascorbate, and 13-cis-retinoic acid. The level of O6MeGua in control rats was 29.9 [(O6MeGua x 10(6)/guanine)]. When rats were fed 0.25% (w/w) DSF, this value was reduced to 10.2, and at 0.5% DSF there was not detectable O6MeGua formed. Injection of pyrazole (40 mg/kg ip) 2 hr prior to 1,2-dimethylhydrazine treatment reduced the O6MeGua level to 2.4. All the other tumorigenesis inhibitors had no effect on either O6MeGua levels or the cpm/mg DNA in treated rats. With O6MeGua as a measure of the extent of initiation, these results confirm that DSF and pyrazole inhibit the initiation phase of carcinogenesis. This is to be expected as both have been shown to block the metabolism of azoxymethane, which is a crucial metabolite in the activation of 1,2-dimethylhydrazine. The other substances, all known tumorigenesis inhibitors, may act on the promotional phase of carcinogenesis and are worthy of further study for their role in cancer prevention. (Author abstract) (22 Refs)

32. QUANTITATION OF A MUTAGENIC METABOLITE PRODUCED FROM 1,2-DIMETHYLHYDRAZINE DURING LIPID INFLUENCED COLON CANCER DEVELOPMENT BY A BACILLUS SUBTILIS ASSAY.

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Diss Abstr Int [B]; 42(4):1330-B 1981

The positive correlation between intake dietary fat and cancer of the colon is well documented. Studies were conducted using an experimental colon carcinogenesis model to determine the role of dietary fat in the metabolism of the colon carcinogen, 1,2-dimethylhydrazine (DMH). Bacillus subtilis TKJ6321 was used to quantify fecal mutagen and postmitochondrial enzyme in the liver and the colon mucosa of rats fed diets variable in lipid content and treated ip with DMH. Corn oil or coconut oil were used as the source of lipid for the diets. During a 32 wk schedule rats were sacrificed and autopsied for evidence of adenocarcinoma of the colon. Fecal samples were extracted and assayed for mutagenic activity by B subtilis TKJ6321 as the microbial detector of mutagenicity. Rats fed corn oil in the diet and treated with DMH produced a significantly higher number of adenocarcinomas of the colon. When the lipid content of the diet was raised to 10% (wt/wt) corn oil markedly stimulated enzyme induction in animals receiving DMH treatment. This induction was especially pronounced in the mutagen-producing enzyme activity of the colonic mucosa. Treatment of rats with DMH induces enzyme in the liver and colon relevant for the conversion of this compound to a mutagenic species. The extent of enzyme activity is influenced by the type of lipid supplementing the diet as is subsequent colon tumor development. (no Refs)

33. BUTYLATED HYDROXYTOLUENE PRETREATMENT REDUCES CYTOTOXICITY AND COVALENT BINDING OF AFLATOXIN B1 IN PRIMARY HEPATOCYTE CULTURES (MEETING ABSTRACT).

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Toxicologist; 1(1):108 1981

Primary cultures of adult rat hepatocytes were used to characterize the effect of butylated hydroxytoluene (BHT) pretreatment on the cytotoxicity and metabolism of a cytotoxic dose of aflatoxin B1 (AFB1). Male Sprague-Dawley rats were divided into two groups of four each, and fed either a control diet or one containing 0.5% BHT. After ten days, hepatocytes were prepared and cultured in chemically-defined, hormone-supplemented medium. After 20-22 hr in culture, 0.12-0.15 ug of [14C] AFB1 were added to dishes containing 2.5 x 10(6) cells. Medium was removed from sets of three cultures at 1/2, 1, 2, 4, 6, 10, and 24 hr thereafter, and extracted with chloroform. Cells were precipitated with 5% TCA and washed exhaustively with organic solvents. After 10 hr, control cells converted 59% of the AFB1 to aqueous metabolites, while 15% was bound covalently. During the same intervals, cells from BHT-fed rats produced 69% aqueous metabolites, and only 6% was bound covalently. AFB1-induced cytotoxicity was much greater in cells from control rats, as evidenced by release of lactate dehydrogenase (LDH) into the medium. Thirty-one hr after addition of AFB1, LDH levels in media from control cells av 1036+/-169 units/ml, while media from BHT-pretreated cells contained only 350+/-45 units/ml. BHT reduces cytotoxicity by apparently increasing the output of relatively nontoxic, water-soluble metabolites and decreasing the output of activated metabolites which covalently bind to macromolecules. Based on results from this in vitro model, we predict the BHT will also protect against AFB1-induced acute toxicity and carcinogenicity in vivo. (no Refs)

34. METABOLISM OF CYCLOPROPENOID FATTY ACIDS AND AFLATOXIN B1 IN ISOLATED HEPATOCYTES OF RAINBOW TROUT (SALMO GAIRDNERI) (MEETING ABSTRACT).

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Toxicologist; 1(1):34 1981

Rainbow trout are the most sensitive animal to Aflatoxin B1 (AFB) hepatocarcinogenicity. AFB1 is a potent carcinogenic mycotoxin occurring in contaminated peanuts, corn, and other grains. Trout feeding studies have also demonstrated the great synergistic hepatocarcinogenicity between AFB1 and cyclopropenoid fatty acids (CPFA). CPFA occur naturally in cotton-seed, kapok, and other food oils. Reason for this synergism has been the subject of much research. Hepatocytes were isolated in high viability (90% lactic dehydrogenase retained) from rainbow trout liver in situ by a two-step collagenase perfusion. Cells were incubated with CPFA and AFB1 and various metabolic parameters assessed. CPFA caused a dose-dependent fall in cellular glutathione (GSH) level, and a concomitant rise in lipid peroxidation occurred even in the absence of added ADP-Fe. The drop in GSH content was slower with CPFA than with diethyl maleate (DEM). Great excesses of either CPFA or DEM were required to significantly decrease cellular GSH. Binding of 3H-AFB1 to DNA was also investigated. AFB1 was rapidly bound to DNA in isolated hepatocytes. A dose of AFB1 added to cells after 0,1,2,3 or 4 hr preincubation resulted in the same level of DNA binding. Benzo(a)pyrene monooxygenase activity also remained constant for 4 hr. Cytotoxicity of AFB1 and the effect of CPFA on AFB1-DNA binding will be presented. (no Refs)

35. THE EFFECT OF DIETARY SELENIUM ON THE METABOLISM AND EXCRETION OF THE HEPATOCARCINOGEN 2-ACETYLAMINOFLUORENE IN THE RAT.

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Diss Abstr Int [B]; 42(4):1412-B 1981

Hepatic enzymes, presumably involved in the metabolism of the hepatocarcinogen 2-acetylaminofluorene (AAF), were examined in rats fed a Torula yeast-based selenium-deficient diet or the same diet supplemented with 0.5 ppm selenium (as sodium selenite). Selenium-deficient rats exhibited almost total absence of hepatic selenium-dependent glutathione peroxidase activity three wk after initiation of test diet feeding. Dietary selenium had no significant effect on hepatic soluble sulfotransferase activity in vitro as measured with the substrates, N-hydroxy-AAF and phenol. Hepatic lipid peroxidation (HLP) was not altered by AAF-challenge in rats fed either diet. In agreement with previous reports, dietary selenium protected against increased HLP produced by administration of carbon tetrachloride. Selenium-supplemented rats exhibited (a) no significant change in the production of 7-,5-, and N-hydroxy-AAF metabolites and (b) significantly increased production of 3-hydroxy-AAF metabolite as compared to selenium-deficient rats. Dietary selenium had no significant effect on total metabolites excreted or on the major phenolic metabolites excreted into the free-glucosiduronic acid-conjugated, or sulfuric acid-conjugated fractions. However, selenium-deficient rats excreted two and three x more N-hydroxy-AAF into the free-, and glucosiduronic acid-conjugated fractions, respectively. These findings tend to support the hypothesis that dietary selenium alters the in vivo metabolism of AAF in a manner that selectively decreases N-hydroxy-AAF excretion, and possibly its production. Thus dietary selenium's protective effect against AAF-induced hepatocarcinogenesis may be partially explained by the ability of selenium to decrease the amount of N-hydroxy-AAF available for further activation. (no Refs)

36. SULFATE-DEPENDENT METABOLIC ACTIVATION OF 2-ACETYLAMINOFLUORENE BY PRIMARY CULTURES OF ADULT RAT HEPATOCYTES (MEETING ABSTRACT).

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Toxicologist; 1(1):35 1981

The role of sulfate in the metabolic activation of the model aromatic amine hepatocarcinogen 2-acetylaminofluorene (2AAF) was determined using primary hepatocyte cultures as a cellular model of the liver. Adult male rat hepatocytes were isolated by collagenase perfusion of the liver and maintained in collagen-coated dishes with hormone-supplemented, chemically defined media. Cytochrome P-450 levels were fully maintained in the cultures for 48 hr. After 28 hr, the cultures were incubated with 67-137 ng of [14C]2AAF. Polar metabolites were isolated by chloroform-water partitioning, and bound carcinogen residues were measured as non-extractable radioactivity incorporated into hepatocellular trichloroacetic-acid-insoluble material. In an experiment using sulfate-free medium, sulfate supplementation doubled the level of bound residues at 2 and 3 1/2 hr but had no effect at 21 hr. Culture media containing 0, 0.1, 0.5 and 1.0 mM sulfate respectively produced 0.8, 1.4, 3.6 and 4.8% bound residues in a 3 hr incubation. Sulfate supplementation did not effect the overall rate of 2AAF metabolism. Phenol, at 1 uM in sulfate-free media, doubled the level of bound residues. Galactosamine, at 2mM, reduced by half the level of bound residues in cultures incubated with 2AAF and 1mM sulfate. These findings support the importance of sulfoconjugation in the metabolic activation of 2AAF. (no Refs)

37. MEMBRANE ALTERATIONS IN FUSING AND PHORBOL ESTER-TREATED MYOGENIC CELLS.

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Diss Abstr Int [B]; 42(4):1431-B 1981

Cultured chick embryo myogenic cells differentiate and fuse to form multinucleated myotubes which become striated and acquire the potential to undergo spontaneous contractions. The diterpene tumor promoter, phorbol-12-myristate 13-acetate (PMA) inhibits myoblast fusion. The most rapid effects of this lipophilic compound occur in plasma membrane-associated processes, such as ion transport and cyclic nucleotide generation. Changes in specific membrane proteins have also been reported to occur in PMA-treated myogenic cells. In addition to the reported alterations in the levels of membrane proteins of known function it was possible that PMA extensively altered the composition and metabolism of other plasma membrane proteins whose functions are unknown. This hypothesis was tested using radiolabeled leucine and mannosamine precursors and electrophoretic analysis of membrane proteins on polyacrylamide gels. By 8 hr incubation PMA altered plasma membrane protein and sialoglycoprotein composition. Stimulation of diacylglycerol levels (2-fold) and stimulation of the rate of label incorporated into phosphatidic acid (2-fold), phosphatidylinositol (3-fold) and phosphatidylcholine (2-fold) were observed within 15-30 min of treatment with PMA. The increase in each of these lipids was shown to arise by synthesis from pre-existing lipids rather than by de novo synthesis. Using a double-label turnover technique and fatty acid analysis, it was shown that phosphatidylcholine is the most probable precursor of the PMA-induced diacylglycerol fraction. Subcellular fractionation of the PMA-stimulated cells suggested that the diacylglycerol was generated in the plasma membrane. Possible models for the mechanisms of PMA-dependent alterations in lipid metabolism and myoblast fusion are discussed. (no Refs)

MUTAGENICITY OF ACTIVATED METABOLITES OF CARCINOGENS

38. LARGE DIFFERENCES IN METABOLIC ACTIVATION AND INACTIVATION OF CHEMICALLY CLOSELY RELATED COMPOUNDS: EFFECTS OF PURE ENZYMES AND ENZYME INDUCTION ON THE MUTAGENICITY OF THE TWELVE MONOMETHYLATED BENZ[A]ANTHRACENES, 7,12-DIMETHYLBENZ[A]ANTHRACENE AND BENZ[A]ANTHRACENE IN THE AMES TEST.

Glatt H, Vogel K, Beatley P, Sims P, Oesch F
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Carcinogenesis; 2(9):813-821 1981

Benz[a]anthracene, 7,12-dimethylbenz[a]anthracene (DMBA), and 12 isomeric monomethylbenz[a]anthracenes were all activated by C3H mice liver preparations to mutagens in Salmonella typhimurium TA100. However, the modes and requirements of metabolic activation differed widely for the different compounds. Some compounds were readily activated by the postmitochondrial liver fraction (S-9 mix) from control mice, but others were activated only by S-9 mix from 3-methylcholanthrene- or phenobarbital-treated mice. All compounds were mutagenic when activated with S-9 mix from Aroclor 1254-treated animals. Purified microsomal epoxide hydrolase almost completely inhibited the mutagenicity of some compounds, but it potentiated that of others, particularly K-region methylbenz[a]anthracenes. Purified cytosolic dihydrodiol dehydrogenase decreased the mutagenicity of the strong carcinogens DMBA, 7-methylbenz[a]anthracene, and 12-methylbenz[a]anthracene by up to 41%. In contrast, the enzyme had relatively moderate effects on the other compounds. None of the activating systems gave a quantitative correlation between mutagenicity and carcinogenicity in whole animal tests. (67 Refs)

39. LUNG AND LIVER CELL-MEDIATED MUTAGENESIS SYSTEMS: SPECIFICITIES IN THE ACTIVATION OF CHEMICAL CARCINOGENS.

Langenbach R, Nesnow S, Tompa A, Gingell R, Kuszynski C
Carcinogenesis and Metabolism Branch (MD 68), Genetic Toxicology Div., Health Effects Res. Lab., US Environmental Protection Agency, Research Triangle Park, NC, 27711
Carcinogenesis; 2(9):851-858 1981

Carcinogens from three chemical classes were compared for mutagenicity in systems containing cocultivated adult Sprague Dawley rat hepatocytes or lung cells and Chinese hamster V79 cells. 7,12-dimethylbenz[a]anthracene (DMBA), 3-methylcholanthrene (MCA), and benzo[a]pyrene (BP) were mutagenic for V79 cells in the lung cell-mediated system. DMBA and MCA were less mutagenic in the liver system, and BP was negative in this system. Aflatoxin B1 was mutagenic in the liver cell system but was only weakly mutagenic in the lung cell system. Dimethylnitrosamine (DMN) was mutagenic only in the presence of liver cells. The metabolism of BP and DMN was investigated to gain insight into the causes of their organ specificity. For DMN, the lack of metabolic activation by rat lung cells apparently accounted for its lack of mutagenicity in the lung cell-mediated system. BP was metabolized by both systems, but quantitative differences were observed in the metabolites detected. Lung cells produced primarily the 7,8-and 9,10-diols and little detectable 4,5-diol, whereas liver cells produced the 4,5-diol as the major metabolite. (38 Refs)

40. METABOLISM OF N-NITROSO-2,6-DIMETHYLMORPHOLINE (NNDM) BY THE VARIOUS COMPONENT CELLS OF HAMSTER PANCREAS (MEETING ABSTRACT).

Scarpelli DG, Rao MS, Kokkinakis D, Hollenberg P
Department of Pathology, Northwestern University Medical School, 303 E. Chicago Avenue, Chicago, IL, 60611
Newsletter Natl Pancreas Cancer Project; VI(2):52 1981

Hamster pancreas contains the necessary enzymes for activation of NNDM and N-nitrosobis(2-oxopropylamine) (NBOP) to forms mutagenic for Salmonella typhimurium. We report here on the metabolism of [3H]NNDM by S-9 and microsomes of whole pancreas (WP), and highly purified fractions of acinar cells (AC), and S-9 of islet cells (IC) isolated from normal and tetrachlorodibenzoparadioxin (TCDD) treated pancreas. Metabolism by duct and ductal cells was established by incubation of pancreatic slices in medium containing NNDM in the presence of [3H] thymidine with and without hydroxyurea to assess DNA repair. Analysis of metabolites by high pressure liquid chromatography showed that S-9 of WP, AC and IC metabolize NNDM to the following sequences of compounds respectively in descending order of concentration: N-nitroso(2-hydroxypropyl-2-oxopropyl)amine (HPOP) greater than NBOP greater than nitrosobis(2-hydroxypropyl)amine (BHP); NBOP greater than HPOP greater than BHP; and NBOP greater than BHP greater than HPOP. Addition of NADPH did not significantly alter metabolism of WP, but for AC led to increased formation of BHP; pretreatment with TCDD increased total metabolism in all instances. Microsomes of WP and AC produced the sequence NBOP greater than BHP greater than HPOP. TCDD increased (78%) total metabolism over that of controls. NADPH led to increased metabolism with both control microsomes (228%) and those isolated from TCDD pretreated animals (212%). Metabolism by S-9 and microsomes isolated from WP, AC and IC were about 1/20 those isolated from liver. Unscheduled DNA synthesis (repair) in nuclei of duct epithelium suggests that these cells are also capable of metabolizing NNDM. (1 Ref)

41. MUTAGENICITY OF ALKYL GLYCIDYL ETHERS IN THREE SHORT-TERM ASSAYS.

Thompson ED, Coppinger WJ, Piper CE, McCarroll N, Oberly TJ, Robinson D
Miami Valley Lab., Procter and Gamble Co., P.O. Box 39175, Cincinnati, OH, 45247
Mutat Res; 90(3):213-231 1981

Effect of alkyl chain length on the mutagenic potential of glycidyl ethers was examined in three in vitro assays, the Salmonella/mammalian microsome assay, the L5178Y mouse lymphoma assay, and by unscheduled DNA synthesis induced in WI38 human diploid fibroblasts. Glycidol, ethyl glycidyl ether, butyl glycidyl ether, and hexyl glycidyl ether were positive in the Salmonella revertant assay with or without metabolic activation, although enhancement of the response was seen in the presence of S9. Octyl glycidyl ether, decyl glycidyl ether, and dodecyl glycidyl ether induced a weak mutagenic response only in the presence of S9. Tetradecyl glycidyl ether was negative in this assay. In the mouse lymphoma assay, glycidol and the ethyl, butyl, and hexyl glycidyl ethers gave positive responses with or without S9. Octyl, dodecyl, and tetradecyl glycidyl ethers were negative. In the unscheduled DNA synthesis assay, positive responses were obtained for glycidol and ethyl glycidyl ether in the presence of S9. Weak responses were obtained for glycidol and ethyl glycidyl ether in the presence of S9. Weak responses were obtained for butyl glycidyl ether with S9 and ethyl glycidyl without S9, but other compounds were negative in this assay. (18 Refs)

42. MUTAGENICITY AND CYTOTOXICITY OF HALOETHANES AS STUDIED IN THE CHO/HGPRT SYSTEM.

Tan EL, Hsie AW
Graduate Sch. Biomedical Sciences, Univ. Tennesee, Oak Ridge, TN
Mutat Res; 90(2):183-191 1981

Mutagenic and cytotoxic effects of ethylene dibromide (EDB), ethylene bromochloride (EBC), and ethylene dichloride (EDC) as quantified in the Chinese hamster ovary cell/hypoxanthine-guanine phosphoribosyl transferase mammallian cell gene mutation assay are reported. All haloethanes tested exhibited mutagenic activity in the presence or absence of S9, in the order EDB greater than EBC greater than EDC. When tested as direct-acting agents, EDM, EBC, and EDC reduced cell survival to 50% at approx 3, 6, and 50 mM, respectively. Cell survival decreased with further increases in haloethane concentration. Cell survival dropped exponentially over a treatment time of 24 hr, but the mutagenic activity attained a max at approx 5 hr. The haloethanes were 5-25x more toxic in the presence of S9 than in its absence. S9-induced toxic metabolites were also more mutagenic to the cells. Such increased toxicity is NADPH-dependent. (22 Refs)

43. MUTAGENIC ACTIVITY IN DIESEL EXHAUST PARTICULATES.

Nachtman JP, Xiao-hai X, Rappaport SM, Talcott RE, Wei ET
Standard Oil Co. California, Richmond, CA, 94802
Bull Environ Contam Toxicol; 27(4):463-466 1981

The mutagenicity of chloroform eluates of diesel exhaust particulate extracts was examined by Ames test with or without S-9 mix. Exhaust eluates produced S-9-independent mutagenic activity of approx 480 revertants/100 ug of extract/plate. The addition of live enzymes decreased mutagenic activity. After reduction of the exhaust extract with sodium borohydride, the S-9-independent activity was greatly diminished. Addition of S-9 to the reduced sample revealed the presence of S-9-dependent mutagenic activity. Results suggest the presence of nitroarene mutagens in diesel exhaust particulates. (12 Refs)

44. MUTAGENICITY OF COSMETICS INGREDIENTS LICENSED BY THE EUROPEAN COMMUNITIES.

Gocke E, King MT, Eckhardt K, Wild D

Zentrallabor fur Mutagenitatsprufung, Deutsche Forschungsgemeinschaft, Breisacher Str. 33, D-7800 Freiburg/Breisgau, W. Germany

Mutat Res; 90(2):91-109 1981

Cosmetic ingredients allowed by the guidelines of the Council of the European Communities (27 July 1976) were investigated for mutagenicity in the Salmonella/microsome assay (SAL-m), the Basc test on Drosophila (Basc), and the micronucleus test on mouse bone marrow (MN). Of the 31 chemicals tested, 15 were mutagenic in SAL-m. Five of these were also mutagenic in Basc and two in the MN test. Only one compound, pyrogallol, was active in all three test systems. None of the compounds positive in the two eukaryotic systems was inactive in the SAL-m assay, which underlines the sensitivity of the Ames test with regard to various mutagens. Of the compounds positive in the SAL-m test, seven would not have been recorded if only the generally used Vogel-Bonner medium had been used. Of these substances, two were mutagenic in one or the other of the two eukaryotic test systems. (62 Refs)

45. MUTAGENICITY IN SALMONELLA OF DYES USED BY DEFENCE PERSONNEL FOR THE DETECTION OF LIQUID CHEMICAL WARFARE AGENTS.

Nestmann ER, Kowbel DJ, Wheat JA

Environmental Health Centre, Tunney's Pasture, Ottawa, Ontario, K1A OL2, Canada

Carcinogenesis; 2(9):879-883 1981

Six indicator dyes capable of detecting chemical warfare agents in liquid form were tested for mutagenicity in the Salmonella typhimurium/rat microsome plate incorporation assay. Ethyl-bis(2,4-dinitrophenyl)acetate, Orasol Navy Blue 2RB (TD-4), and Eastman Fast Blue G-BLF induced dose-related increases in His+ reversion mutations in three or more of the S typhimurium tester strains (TA153, TA100, TA1537, TA1538, and TA98). Papers in which the dyes were impregnated were also mutagenic. Thiodiphenyl-4,4'-diazo-bis-salicylic acid was weakly mutagenic in the plate assay but strongly mutagenic in a fluctuation assay. Fluorescent Brilliant Yellow R and 2,5,2',5'-tetramethyltriphyenyl methane-4,4'-diazo-bis-beta-hydroxynaphthoic anilide were not mutagens. (16 Refs)

BINDING OF CARCINOGENS AND THEIR METABOLITES TO MACROMOLECULES

46. FORMATION OF COVALENT DEOXYRIBONUCLEIC ACID BENZO(A)PYRENE 4,5-EPOXIDE ADDUCT IN MOUSE AND RAT SKIN.

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Cancer Lett; 14(2):125-129 1981

The formation of benzo(a)pyrene DNA adducts was determined 24 hr after topical administration of labeled compound to the backs of female Swiss mice and male Wistar rats. Adducts corresponding to authentic 4,5-dihydro-4,5-epoxy benzo(a)pyrene standards and to a further metabolite of 9-hydroxybenzo(a)pyrene were identified via high pressure liquid chromatography. (17 Refs)

47. BENZO(A)PYRENE METBOLISM AND COVALENT BINDING OF BENZO(A)PYRENE METABOLITES TO DNA.

Shen AL
University of Wisconsin, Madison, WI
Diss Abstr Int [B]; 42(3):880-B 1981

Benzo(a)pyrene metabolism and covalent binding of benzo(a)pyrene metabolites to DNA have been investigated in liver microsomes and hepatocytes prepared from 3-methylcholanthrene treated rats and in C3H/10T1/2/CL8 mouse embryo fibroblasts. In both hepatocytes and microsomal incubations, the major benzo(a)pyrene DNA adducts formed were adducts of anti- and syn- isomers of (-)-trans-7,8-dihydroxy-9,10-epoxy-7,8,9,10 tetrahydrobenzo(a)pyrene (diol-epoxides) and of epoxide derivatives of benzo(a)pyrene-9-phenol (phenol-oxides). Diol-epoxide adducts predominated in hepatocytes while the reverse was found in microsomal incubations. C3H/10T1/2/CL8 fibroblasts metabolized benzo(a)pyrene to products which bound covalently to DNA. The major adducts were those arising from anti- and syn-benzo(a)pyrene diol-epoxides. (no Refs)

48. METABOLISM OF BENZO[A]PYRENE BY HUMAN MAMMARY EPITHELIAL CELLS: TOXICITY AND DNA ADDUCT FORMATION.

Stampfer MR, Bartholomew JC, Smith HS, Bartley JC
(c/o Bartley) Peralta Cancer Res. Inst., Peralta Hosp., 3023 Summit St., Oakland, CA, 94609
Proc Natl Acad Sci USA; 78(10):6251-6255 1981

Pure cultures of human breast epithelial cells and of fibroblastic cells in early passage provided the opportunity to ask whether either cell type had the capability for metabolizing chemical carcinogens and, if so, was the fate of the metabolic products compatible with chemical carcinogens being a factor in the initiation of breast cancer in women. For this purpose, cells were exposed to benzo[a]pyrene (BaP), and (i) the influence on growth potential and (ii) the extent, type, and persistence of adducts between the metabolites of BaP and DNA were measured. Compared with fibroblasts, inhibition of growth by epithelial cells was 50-100x more sensitive to BaP. Because of this differential sensitivity, epithelial cells were exposed to 4.0 uM BaP and fibroblasts were exposed to 4.0 uM BaP in the studies of DNA adduct formation. Separation by high-pressure liquid chromatography of adducts between (+-)-7,8-dihydroxy-9,10-expoxy-7,8,9,10 tetrahydrobenzo[a]pyrene (BaP diol epoxide) and nucleosides from purified DNA revealed that epithelial cells contained modified DNA within 6 hr after adding BaP. Adducts between the 7R anti stereoisomer of BaP diol epoxide and deoxyguanosine predominated at all times. syn BaP diol epoxide adducts with deoxyguanosine and what appeared to be BaP diol epoxide adducts with deoxycytidine were consistently present but at much lower frequency. All three types of BaP diol epoxide-DNA adducts persisted in epithelial cells for 72 hr in BaP-free medium. No adducts were detected in fibroblastic cultures until 96 hr after first exposure to BaP. At this time, the type and extent of BaP diol expoxide-DNA adduct formation was similar to that in epithelial cells exposed to one-tenth the dose of BaP. The type, extent, rate of formation, and persistence of the adducts in human breast epithelial cells was similar to that in cells transformable by exposure to BaP, an indication that they may be targets for chemically induced carcinogenesis. (Author abstract) (42 Refs)

49. ACTIVATION AND DETOXIFICATION OF BENZO(A)PYRENE BY HAMSTER AND RAT HEPATOCYTES (MEETING ABSTRACT).

Raineri R, Poiley JA, Pienta RJ
Frederick Cancer Research Center, Frederick, MD, 21701
In Vitro; 17(3):222 1981

The ability of hepatocytes from Syrian golden hamsters and Sprague-Dawley rats to metabolize and covalently bind [3H]-benzo(a)pyrene (BP) was examined. Following 3 hr incubation with 4.4 uM BP, hamster hepatocytes metabolized 95% of the BP; rat hepatocytes only 41%. There were 5 x more water-soluble metabolites in the medium from hamster than from rat hepatocytes. The levels of organic solvent-soluble metabolites (OSM) were similar. While beta-glucuronidase treatment of hamster hepatocyte medium increased the OSM, no such increase was seen after treatment of rat hepatocyte medium. The results were similar after treatment with arylsulfatase. When hepatocytes from Aroclor 1254 (AC)-treated animals were compared, increases in OSM after enzymatic deconjugation occurred only with hamster preparations. A 5-fold increase in levels of binding of BP to hamster hepatocyte RNA, and a 17-fold increase to rat RNA, occurred when hepatocytes from AC-treated animals were used. Increased levels of binding to rat hepatocyte DNA and protein were also seen. Although BP is not considered a liver carcinogen, we found high rates of conjugation and binding in liver cells. Initial metabolism may therefore occur in the liver followed by transport of conjugated metabolites and subsequent activation at the site of tumor induction. (no Refs)

50. THE EFFECT OF AN INDIVIDUAL'S BLOOD PRESSURE ON THE PERCENTAGE OF TOTAL 7,12-DIMETHYLBENZ[A]ANTHRACENE METABOLITES THAT BIND COVALENTLY TO DNA IN CULTURED RESTING LYMPHOCYTES.

Pero RW, Bryngelsson C, Ostlund C, Bryngelsson T, Norden A
Unit Community Care Sciences, S-240 10 Dalby, Sweden
Chem Biol Interact; 37(1):1-12 1981

A method for the quantitative analysis of the percent metabolism that results in covalent binding of 7,12-dimethylbenz[a]anthracene (DMBA) to DNA in viable resting human lymphocytes is described. The inter- and intra-experimental reproducibility as judged by the coefficient of variation and examined in the same individual over a 3-mo period was 31.4% and 13.9%, respectively. When the lymphocytes from 30 hypertensive individuals were exposed to 1 uM DMBA for 18 hr, the percent of total DMBA metabolites that bind DNA covalently was correlated to the blood pressures of the patients at the time of sampling (r = 0.53, p less than 0.005). No influences on the data from the type or duration of hypertensive drug treatment could be statistically determined for this sample of hypertensive patients. It was concluded that high blood pressure is a strong determinant in predisposing lymphocytes to increased genetic risk from induced DNA damage and that this relationship is not statistically affected by hypertensive drug therapy. (Author abstract) (33 Refs)

51. THE DETERMINATION OF O(6)-METHYL- AND 7-METHYLGUANINE IN MOUSE LIVER DNA FROM DIMETHYLNITROSAMINE-TREATED MICE BY HIGH-PERFORMANCE LIQUID CHROMATOGRAPHY WITH UV ABSORBANCE DETECTION.

Lawrence JF, Leduc R, Ryan JJ
Food Res. Div., Health Protection Branch, Tunney's Pasture, Ottawa K1A 0L2, Ontario, Canada
Anal Biochem; 116(2):433-438 1981

The methylated purines O6-methyl- and 7-methylguanine were isolated from mouse liver DNA hydrolysates by means of a column cleanup employing a Sep Pak C-18 reverse-phase cartridge. The purine bases were eluted from the cartridge with methanol, evaporated to dryness, and then dissolved in mobile phase for liquid chromatographic analysis by normal-phase chromatography. The system consisted of a LiChrosorb Si 60 column with a water-saturated mobile phase of 20% methanol in chloroform containing 0.001% H3PO4. The two methylated bases eluted before adenine or guanine. For extremely low-level (less than 300 pmol) quantitation, the peaks corresponding to O6-methyl- and 7-methylguanine were collected and then analyzed by reverse phase chromatography with LiChrosorb RP-18 column and mobile phase of 5% methanol in pH 7 phosphate buffer (for 7-methylguanine) or 9.5% methanol/buffer (for O6-methylguanine). Comparisons were made with fluorescence detection and with scintillation counting (in animal studies where [14C]dimethylnitrosamine was used). Minimum detectable levels at 254 nm were about 3 ng (3:1 signal to noise ratio) for each of the title compounds. As low as 10 pmol/mg of each could be detected in DNA hydrolysates. Recoveries of O6-methyl- and 7-methylguanine from DNA spiked at 750 pmol/mg were greater than 80%. (Author abstract) (20 Refs)

52. INDUCTION OF PANCREATIC DNA DAMAGE AND TUMORS IN RATS TREATED WITH N-NITROSO-BIS(2-OXOPROPYL)AMINE (MEETING ABSTRACT).

Longnecker DS, Zurlo J, Curphey TJ
Department of Pathology, Dartmouth Medical School, Hanover, NH, 03755
Newsletter Natl Pancreas Cancer Project; VI(2):35 1981

Differences in response of various species to carcinogens pose problems in regard to extrapolation from animal experiments to man. In experimental pancreatic carcinogenesis, several oxidized derivatives of dipropylnitrosamine have been effective pancreatic carcinogens in hamsters whereas they have failed to induce pancreatic cancers in rats. In studying this species difference we have used alkaline elution analysis to demonstrate DNA damage in pancreas of rats treated with N-nitrosobis(2-oxopropyl)amine (BOP) and N-nitroso-(2-hydroxypropyl-2-oxopropyl)amine (HPOP). Because these agents were effective in inducing DNA damage in pancreas, we treated young rats with a single dose of BOP (100 mg/kg) or HPOP (20 mg/kg) and autopsied them 4 mo later. Grossly visible nodules measuring up to 3 mm were present in pancreases of rats of both groups. Histologically the pancreases contained multiple foci and nodules of atypical acinar cells which were not seen in controls. Thus, BOP and HPOP induce both DNA damage and phenotypic changes in acinar cells in rats which are similar to those induced by the pancreatic carcinogens azaserine and Ndelta-(N-methyl-N-nitrosocarbamoyl)-L-ornithine. Although rats appear to be less sensitive than hamsters to BOP, both species respond to comparable doses of HPOP. Our findings suggest that these compounds would induce pancreatic cancers in rats in studies of 1-2 yr duration if appropriate doses are given to young rats. (no Refs)

53. STUDIES ON NITROSAMINE METABOLISM. III. COMPARISON OF THE SUBCELLULAR DISTRIBUTION OF RADIOACTIVITY IN TISSUES OF RFM AND BALB/C MICE FOLLOWING ADMINISTRATION OF [14C]DIETHYLNITROSAMINE.

Daugherty JP, Clapp NK
Comprehensive Cancer Center, Univ. Alabama Sch. Medicine, Birmingham, AL, 35294
Res Commun Chem Pathol Pharmacol; 34(1):165-168 1981

The tissue distribution of radioactivity in male RFM and BALB/c mice was investigated following a single dose of [14C]-labeled diethylnitrosamine (DEN). The radiolabel was associated with all the subcellular fractions, and the majority of the radioactivity was located in the cytosol fraction. The majority of the radiolabel was usually eliminated from the fractions within 16-24 hr after [14C]DEN administration. (Author abstract) (4 Refs)

54. POTENCY OF AFLATOXIN B1 AND AFLATOXIN M1 IN CYTOTOXICITY AND DNA REPAIR ASSAYS (MEETING ABSTRACT).

Green CE, Rice DW, Hsieh DP, Byard JL
Department of Environmental Toxicology, University of California, Davis, CA, 95616
Toxicologist; 1(1):42 1981

Although the acute toxicity and carcinogenicity of aflatoxin B1 (AFB1) has been thoroughly documented, relatively little is known of the potency of aflatoxin M1 (AFM1), a hydroxylated metabolite of AFB1. Therefore, the cytotoxicity and genotoxicity of AFB1 and AFM1 were compared using in vitro system of primary cultures of rat hepatocytes. Hepatocytes were cultured for 20 hr (2.5 x 10(6) cells/dish) in hormone supplemented culture medium. The incubation was continued for an additional 24 hr with the test chemicals and 0.5 uCi/ml [3H] thymidine ([3H]TdR). Cytotoxicity was assessed by measuring lactate dehydrogenase- released into the culture medium. Both AFB1 and AFM1 were potent cytotoxins. LDH levels were elevated significantly above controls for AFB1 at 0.1 ug/dish and for AFM1 at 0.6 ug/dish. However, LDH concentrations rose to the same max of approx 200% of controls for AFB1 and AFM1 at a dose of 1.2 ug/dish. Genotoxicity was assessed by measuring unscheduled DNA synthesis by two different methods, incorporation of [3H] TdR into trypsin-resistant acid-precipitable material and autoradiographic analysis. AFB1 and AFM1 were both positive and about equally potent in the DNA repair assay using either technique. In vivo experients indicate a higher level of DNA binding for AFb1 than AFM1. There are two plausible explanations for the DNA repair data; 1) AFB1 and AFM1 bind to DNA to approx the same extent in the hepatocyte culture system, 2) less AFM1 is covalently bound to DNA than AFB1 but AFM1 adducts are more efficiently repaired. (1 Ref)

55. ACTIVATION OF N-2-ACETYLAMINOFLUORENE BY TARGET AND NONTARGET SYRIAN GOLDEN HAMSTER CELLS (MEETING ABSTRACT).

Poiley JA, Raineri R, Ernst MK, Andrews AW, Pienta RJ
Frederick Cancer Research Center, Frederick, MD, 21701
In Vitro; 17(3):222 1981

The ability to metabolize and activate N-2 acetylaminofluorene (AAF) of Syrian golden hamster kidney, bladder, small intestine, lung and liver cells was compared with that of hamster embryo fibroblasts. At varying times after isolation, cells were exposed to 5 ug [14C]-AAF for 3, 6 or 24 hr. The level of AAF remaining and the amount bound to cellular components were determined. Within 3 hr, hepatocytes and intestinal cells had metabolized 95% of the AAF. Within 6 hr lung cells had metabolized 50%, and kidney cells 20%. By contrast, fibroblasts and bladder cells had metabolized only 20-25% in 24 hr. The amount of material bound to cellular components was proportional to the amount of AAF metabolized. A second measure of activation was the ability of intact organ cells to metabolize AAF to a form mutagenic in Salmonella TA 1538. Revertant numbers were much increased above background with hepatocytes (240-fold), lung cells (11-fold), intestinal cells (5-fold) and kidney cells (2-fold). With bladder cells and fibroblasts, revertant numbers were not significantly higher. We have demonstrated that intact cells, whether or not from the target organ, can metabolize AAF at a high rate to forms which either bind to cellular components or are excreted. These forms are also mutagenic in Salmonella. (no Refs)

56. PROSTAGLANDIN SYNTHETASE CATALYZED DNA STRAND BREAKS BY AROMATIC AMINES (MEETING ABSTRACT).

Rahimtula A, Moldeus P, Nordenskjoeld M, Andersson B
Memorial University of Newfoundland, Newfoundland, Canada
International Conference on Prostaglandins and Cancer, August 30-September 2, 1981, Washington, DC. Lombardi Cancer Center 75 pp., 1981.

Several aromatic amines are renal medullary toxins and bladder carcinogens. We have found that the aromatic amines 2-naphthylamine, 2-4-diaminotoluene, p-aminophenol and p-phenetidine at a concentration of 50uM cause a 2-3 fold increase in DNA strand breaks in cultured human fibroblasts in the presence of sheep vesicular gland microsomes and arachidonic acid. Indomethacin and butylated hydroxyanisole inhibited this reaction. Curiously, benzidine did not give rise to a significant increase in DNA strand breaks. Metabolism of these amines by prostaglandin synthetase was judged by their ability to complete with and inhibit another prostaglandin synthetase dependent reaction - the activation of paracetamol. An 0.1 mM concentration of these amines inhibited the glutathione conjugate formation of paracetamol by 60-90%. Covalent protein binding of [3H]paracetamol was similarly inhibited. At the concentration used, these amines did not significantly affect the cyclooxygenase activity as judged by prostaglandin E2 and prostaglandin F2alpha formation. (2 Refs)

57. PROSTAGLANDIN SYNTHETASE MEDIATED ACTIVATION OF P-DIMETHYLAMINOAZOBENZENE (BUTTER YELLOW) (MEETING ABSTRACT).

Vasdev S, Tsuruta Y, O'Brien P
Department of Biochemistry, Memorial University of Newfoundland, Newfoundland, Canada
International Conference on Prostaglandins and Cancer, August 30-September 2, 1981, Washington, DC. Lombardi Cancer Center 75 pp., 1981.

The oral administration of dimethylaminoazobenzene (DAB) induces rodent liver tumors, mouse lung tumors and dog bladder tumors. It is believed that the activation by the liver of DAB involves liver microsomal mixed function catalyzed sequential N demethylation and N hydroxylation reactions. A cytosolic sulfotransferase then catalyzed the conjugation of the N-OH derivative with sulfate to form an electrophilic species which can bind to nucleic acids and protein. This electrophile is considered to be the ultimate carcinogenic metabolite. An alternative metabolic activation should now be considered. It has been found that prostaglandin synthetase can catalyze the binding of C14 DAB to microsomal protein. Extensive N demethylation occurred and C14 4-methylaminoazobenzene was much more effective at binding to the protein than DAB. Arachidonate was also more effective than NADPH with mouse lung and dog bladder microsomes. Cumene hydroperoxide was also much more effective than NADPH with rat liver microsomes. However, cytochrome P 450 was the catalyst for the latter hydroperoxide reaction as in this case extensive 4'hydroxylation also occurred. (no Refs)

58. METABOLISM AND MACROMOLECULAR BINDING OF THE CARCINOGEN MICHLER'S KETONE IN RATS.

Struck RF, Shih TW, Johnston TP, Kirk MC, Hill DL
Kettering-Meyer Lab., Southern Res. Inst., Birmingham, AL, 35255
Xenobiotica; 11(8):569-577 1981

Studies on the metabolism of 14C-Michler's ketone (4,4'-bis-(dimethylamino)[carbonyl-14C]benzophenone) in rats have revealed that this carcinogen is subject to demethylation, ring-hydroxylation and N-acetylation after adjacent methyl groups have been removed. As identified by mass spectral analysis, microsomal metabolites are the mono-, di-, tri- and tetra-demethylated derivatives. The major metabolites appearing in the bile are the di- and tri-demethylated derivatives and the N-acetylated tetra-demethylated compound; minor metabolites, tentatively identified, are the ring-hydroxylated derivatives of di- and tri-demethylated Michler's ketone and of N-acetylated tri- and tetra-demethylated Michler's ketone. The major urinary metabolite is tentatively identified as a ring-hydroxylated derivative of N-acetylated, di-demethylated Michler's ketone; a minor urinary metabolite lacks the hydroxyl group. Injection of 14C-Michler's ketone into rats resulted in the irreversible binding of radioactivity to liver proteins. When the rats were pretreated with phenobarbital, this binding was increased and extended to proteins of some other tissues and to DNA and RNA of liver and DNA of kidney. (Author abstract) (13 Refs)

59. PROSTAGLANDIN HYDROPEROXIDASE-MEDIATED 2-AMINO-4-(5-NITRO-2-FURYL)[14C]THIAZOLE METABOLISM AND NUCLEIC ACID BINDING.

Mattammal MB, Zenser TV, Davis BB
(c/o Zenser) Geriatric Center (111G-JB), Veterans Admin. Medical Center, St. Louis, MO, 63125
Cancer Res; 41(12):4961-4966 1981

Prostaglandin hydroperoxide-mediated metabolism and binding of 2-amino-4-(5-nitro-2-furyl)[14C]thiazole ([14C]ANFT) metabolite to nucleic acids and proteins were investigated with rabbit bladder transitional epithelial and solubilized ram seminal vesicle microsomes. Metabolism was assessed by spectrophotometric and radiochemical techniques. Substrate and inhibitor studies are consistent with both metabolism and binding of [14C]ANFT occurring by the prostaglandin hydroperoxidase activity of prostaglandin endoperoxide synthetase. The ratio of the rates of [14C]ANFT product formation is approx 3:7:10 (organic soluble:non-trichloroacetic acid precipitable: trichloroacetic acid precipitable) over a wide range of arachidonic acid concentrations. Approx 2 and 1% of the total [14C]ANFT metabolized binds to transfer RNA and DNA, respectively. The metabolite isolated from the organic phase had a chromatographic profile and UV spectra different from authentic ANFT. If transfer RNA or DNA is added at the end of a 5-min incubation , no binding to nucleic acids was observed. The demonstration of prostaglandin hydroperoxidase-mediated covalent binding to nucleic acids is consistent with the involvement of this enzyme in 5-nitrofuran-induced bladder carcinogenesis. (Author abstract) (44 Refs)

60. IN VITRO METABOLISM OF ACRYLONITRILE TO 2-CYANOETHYLENE OXIDE, REACTION WITH GLUTATHIONE, AND IRREVERSIBLE BINDING TO PROTEINS AND NUCLEIC ACIDS.

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Cancer Res; 41(12):4925-4933 1981

The metabolism of the suspected carcinogen acrylonitrile was studied using subcellular fractions isolated from rats and humans. Irreversible binding of radioactive label from [1-14C]- or [2,3-14C]acrylonitrile to protein and DNA was enhanced by reduced nicotinamide adenine dinucleotide phosphate in the presence of rat liver microsomes or a reconstituted cytochrome P-450 system. During the reduced nicotinamide adenine dinucleotide phosphate-dependent reaction, HCN was produced, and the heme of cytochrome P-450 was destroyed. Rat brain microsomes did not produce detectable levels of metabolites. Conclusive evidence of metabolically mediated binding of acrylonitrile to protein and DNA in human systems was not found. With rats, metabolism was induced by pretreatment of animals with either phenobarbital or 5,6-benzoflavone. Labeled 2-cyanoethylene oxide was found to bind irreversibly to calf thymus DNA and microsomal protein. The extent of binding was greater in the case of 2,3-14C-labeled than 1-14C-labeled material. The relative first-order rate of acrylonitrile binding to calf thymus DNA in rat liver microsomal systems was one to two orders of magnitude less than that for 1,1,2-trichloroethylene and three orders of magnitude less than that for vinyl chloride or vinyl bromide. Rat liver microsomes or a reconstituted cytochrome P-450 system catalyzed the mixed-function oxidation of acrylonitrile to 2-cyanoethylene oxide. 2-Cyanoethylene oxide has a half-life of about 2 hr in neutral buffer at 37 C. This epoxide was found to serve as a substrate for microsomal epoxide hydrolase. HCN was released during hydrolysis of 2-cyanoethylene oxide or reaction of the epoxide with reduced glutathione; however, HCN release in either case was not stoichiometric with epoxide disappearance. 2-Cyanoethylene oxide reacted less rapidly with reduced glutathione than did acrylonitrile. Rat liver cytosol preparations contained glutathione S-transferase activity towards acrylonitrile and greater activity with 2-cyanoethylene oxide as a substrate. Cytosol preparations from rat brain and human liver had no detectable glutathione S-transferase activity towards acrylonitrile but did exhibit some activity towards 2-cyanoethylene oxide. These studies establish the basic pathways involved in the metabolism of acrylonitrile and should provide a basis for examination of the relevance of these individual steps and their roles in bioactivation and detoxication under more physiological situations. (Author abstract) (40 Refs)

61. THE MOLECULAR BASIS FOR COMPLEXATION OF ADRIAMYCIN WITH FLAVIN MONONUCLEOTIDE AND FLAVIN ADENINE DINUCLEOTIDE.

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Dept. Pharmacology, Northwestern Univ. Medical Sch., Chicago, IL, 60611
Arch Biochem Biophys; 212(1):20-36 1981

A molecular level investigation of the interaction of anthracycline (ATC) antibiotics with flavin mononucleotide (FMN) and flavin adenine dinucleotide (FAD) was conducted in view of the potential significance of such reactions in cardiotoxicity and drug metabolism and the ability of NADPH-cytochrome P-450 reductase to most effectively catalyze the reduction of adriamycin (ADM) with electron transfer via the FMN (or FAD) prosthetic group. The nature, strength, and specificity of ADM complex formation with FMN or FAD was studied. Results indicated that ADM can produce saturable, temperature- and concentration-dependent shifts of certain proton resonances of FMN and FAD to high field. The structures of FMN, FAD, and ADM in soln, as well as the mechanism of self-association, are requisite to the development of a molecular model for the ADM-FMN or the ADM-FAD complex. The most likely configuration assumed for the FMN-ADM complexation positions the planar rings of ADM over the aryl ring of FMN such that maximal ring current effect is experienced by the H-9 proton of FMN. A similar orientation is expected for the FAD-ADM complex. The formation of bimolecular complexes between the flavins and ADM, such that the ADM quinone moiety is positioned above the aromatic rings of isoalloxazine, appears to be consistent with the activity of flavoprotein reductases toward ADM. Cytochrome P-450 reductase exhibits a 30-fold greater activity towards ATC reductive glycosidic cleavage than the next most active reductase enzyme, xanthine oxidase, which contains only FAD as its prosthetic group. It was a suggested that a correlation may exist between the formation of molecular level complexes involving ATC antibiotics and FMN or FAD, the metabolic generation of ATC-free radicals, and reactive oxygen species and ATC-induced cardiotoxicity. (43 Refs)

62. IN VITRO AND IN VIVO COVALENT BINDING OF THE KIDNEY TOXICANT AND CARCINOGEN TRIS(2,3-DIBROMOPROPYL)-PHOSPHATE.

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Dept. Toxicology, Natl. Inst. Public Health, Postuttak, Oslo 1, Norway
Toxicology; 21(4):291-304 1981

Incubation of 3H-tris(2,3-dibromopropyl)-phosphate (TRIS-BP) with rat liver microsomes led to its activation to products which bound covalently to microsomal protein. The reaction was NADPH -dependent, and boiled microsomes yielded no binding. The reaction could be inhibited by nitrogen; carbon monoxide, which inhibits cytochrome P-450-mediated reactions, also reduced binding rates significantly. SKF 525-A and metyrapone, a selective inhibitor of phenobarbital-inducible cytochrome P-450, inhibited TRIS-BP activation. Alpha-napthoflavone, a selective inhibitor of cytochrome P-448, had little effect. Addition of glutathione and N-acetylcysteine markedly inhibited binding, but ascorbic acid did not. Paraoxon, an esterase inhibitor, and 1,1,1-trichloropropene-2,3-epoxide and cyclohexene oxide also were without effect. Rat kidney microsomes were capable of activating TRIS-BP to 8% of the level achieved by rat liver microsomes. Administration of TRIS-BP to rats resulted in considerable binding to kidney proteins, with lesser amounts detected in liver and very little in muscle proteins. Liver microsomes activated TRIS-BP to bind to DNA in vitro, but kidney microsomes did not. (31 Refs)

63. SPECIES DIFFERENCES IN MUTAGENICITY, COVALENT PROTEIN BINDING AND NEPHROTOXICITY OF THE FLAME RETARDANT TRIS(2,3-DIBROMOPROPYL) PHOSPHATE (MEETING ABSTRACT).

Soderlund E, Dybing E, Nelson SD
Department of Toxicology, National Institute of Public Health, Olso, Norway
Acta Pharmacol Toxicol; 49(Suppl1):48 1981

Tris(2,3-dibromopropyl)phosphate (Tris-BP), the major flame retardant formerly used in US sleepwear, is a potent mutagen, a nephrocarcinogen and an acute nephrotoxin. Hepatic microsomes from rats, mice, hamsters, and guinea pigs are all able to activate Tris-BP to mutagenic products in the Salmonella microsome quantitative reversion assay, mice microsomes being the most and guinea pig microsomes the least active. Phenobarbital (PB)-pretreatment increases the mutagenic activity with all microsomal preparations, whereas 3-methylcholanthrene (MC)-pretreatment decreases Tris-BP mutagenicity in rats and mice and gives a moderate increase in hamsters and guinea pigs. Hepatic microsomes from all species tested have approx similar basal capabilities in converting Tris-BP to covalently protein bound products in vitro; PB-pretreatment increases binding rates in all preparations, MC-pretreatment increases Tris-BP covalent binding with hamster and guinea pig microsomes but not with microsomes from rat or mouse liver. Tris-BP binds covalently to liver protein in vivo in all species and to kidney protein in hamster, guinea pig and mouse to the same degree. In rat kidneys, on the other hand, seven fold higher protein binding levels are found compared to liver, correlating with the finding that kidney is the target organ in this species. None of the other species showed any Tris-BP-induced kidney damage. (no Refs)

64. THE MULTIPLE ROLES OF ESTROGEN IN ESTROGEN-DEPENDENT RENAL CLEAR-CELL CARCINOMA OF SYRIAN HAMSTER (MEETING ABSTRACT).

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Growth of Cells in Hormonally Defined Media, September 1-4, 1981, Cold Spring Harbor, New York Cold Spring Harbor Laboratory 101 pp., 1981.

Estrogen (estradiol [E2] or diethylstilbestrol [DES]), when implanted subcutaneously into male Syrian hamster, elicits renal clear-cell carcinoma after approx 6-8 mo. Estrogen alone causes this effect, ie no cocarcinogen is required for tumor initiation or growth response. Studies conducted in our laboratories and elsewhere indicate that the elevated level of estrogen in the hamster results in a variety of different responses and biochemical effects which in a concerted fashion lead to the phenomenon called renal clear-cell carcinoma. DES and E2 induce peroxidase activity and microsomal P450 enzymes in a variety of tissues. In turn, peroxidase and microsomal P450 enzymes oxidize DES to a quinoid structure. DES quinone, a chemically unstable and reactive substance, may spontaneously rearrange to beta-dienestrol or, in the vicinity of cellular macromolecules, may covalently bind to DNA. DES-DNA adduct formation was studied in vitro under various conditions. H301 tumor cells, which are derived from the estrogen-dependent renal clear-cell carcinoma of Syrian hamster, remain estrogen-dependent in culture or in host animals. Upon removal of the hormone implant, tumors immediately shrink in size and disappear within 10 days. Estrogen concentration in tumor tissue is low (12-30% of estrogen uptake of liver), despite the presence of estrogen receptors in tumor tissue. (no Refs)

65. METABOLIC ACTIVATION OF DIETHYLSTILBESTROL BY PROSTGLANDIN SYNTHETASE AS A MECHANISM FOR ITS CARCINOGENICITY (MEETING ABSTRACT).

Bennett S, Marshall W, O'Brien PJ

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International Conference on Prostaglandins and Cancer, August 30-September 2, 1981, Washington, DC. Lombardi Cancer Center 75 pp., 1981.

The synthetic estrogen diethylstilbestrol (DES) induces kidney tumors in hamsters and genital tract tumors in rodents. Cervicovaginal alterations including carcinoma were also observed in the female offspring of DES treated women, as were certain teratogenic changes in the genital tract of their male progeny as a result of its transplacental toxicity. Metzler et al 1978 have suggested that peroxidases of estrogen target organs are responsible by catalyzing DES oxidation to intermediate that bind to nucleic acids and other cellular macromolecules. Our research shows that prostaglandin synthetase could also be a catalyst. Seminal vesicular microsomes and uterine microsomes readily catalyzed the binding of C14 diethylst ilbestrol to DNA and protein in the presence of arachidonate but not NADPH. Similar results were obtained with C14 estradiol and could explain the association of estrogens and cancer of tissues whose growth is effected by estrogen. DES also induces liver necrosis in vivo. Blackburn et al 1977 have shown that liver microsomes with NADPH catalyzes the binding of DES to DNA. We have also found that cumene hydroperoxide is much more effective than NADPH in catalyzing this binding. (no Refs)

66. THE INVOLVEMENT OF PROSTAGLANDIN INTERMEDIATES IN COVALENT BINDING TO NUCLEIC ACIDS AND IN AGEING PIGMENT FORMATION (MEETING ABSTRACT).

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Department of Biochemistry, Memorial University of Newfoundland, Newfoundland, Canada
International Conference on Prostaglandins and Cancer, August 30-September 2, 1981, Washington, DC. Lombardi Cancer Center 75 pp., 1981.

Eling et al 1979 have shown that incubation of 1-C14 arachidonic acid with the microsomes of platelets, guinea pig lung, rabbit kidney and rat stomach fundus results in substantial binding to the protein. We also find that prostaglandin synthetase catalyzes the binding of arachidonate to exogenous DNA and RNA to form a fluorescent product. Prostaglandin could therefore play some role in carcinogenesis. The binding of prostaglandin intermediates to microsomal protein resulted in extensive crosslinking and polymerization of some proteins. This was prevented by glutathione or antioxidants and suggests that free radicals were involved. The formation of fluorescent products in the microsomes was attributed to conjugated schiff base product formation from the reaction between phospholipid amines and aldehyde. The spectra was similar to lipofuscin. In vivo lipofuscin pigment formation has been associated with aging, vitamin E deficiency, polyunsaturated fatty acid feeding and the ingestion of various environmental xenobiotics. The various tissues involved were lung, liver, heart, spleen, brain, kidney and testis. Incubation of the microsomes from these tissues with arachidonate resulted in protein polymerization and fluorescence formation. (no Refs)

ALTERATION OF MIXED FUNCTION OXIDASES BY CARCINOGENS

67. METABOLIC ACTIVATION IN TYPE II ALVEOLAR LUNG CELLS OF THE RAT WITH EXPOSURE TO BENZO(A)PYRENE (MEETING ABSTRACT).

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In Vitro; 17(3):201 1981

L-2 cells clonally derived from adult rat lungs with characteristics of type II pneumonocytes exhibited elevated aryl hydroxylase (AHH) and epoxide hydratase (EH) activity following exposure to benzo(a)pyrene [B(a)P]. Max AHH activity was measured fluorometrically at 24 hr and increased linearly over this time period. Peak AHH activity was 10 x that of basal levels while peak EH activity w as about twice basal levels. Nuclear AHH activity was 10 percent that of the whole cells. Theophylline inhibited AHH activity and binding of tritium-labeled metabolites to nuclear macromolecules whereas the prostaglandin synthetase inhibitors indomethacin and sodium meclofenamate stimulated AHH activity and binding of labeled metabolities to nuclear macromolecules. Both the organic and water soluble metabolites extracted from the culture medium failed to produce mutagenesis in four strains of Salmonella typhymurium and in Chinese hamster V-79 cells. Unscheduled DNA synthesis was not observed in L-2 cells exposed to B(a)P. These results suggest that the enzyme activation and subsequent metabolism of benzo(a)pyrene in L-2 cells yields nonmutagenic and noncarcinogenic products and if representative may offer a partial explanation for the low incidence of type II cell involvement in human lung cancer. (1 Ref)

68. CHARACTERIZATION OF BENZOPYRENE HYDROXYLASE ENZYME ACTIVITY IN RAT PANCREAS (MEETING ABSTRACT).

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Medical Research Service, Veterans Administration Medical Center, Augusta, GA, 30912
Newsletter Natl Pancreas Cancer Project: VI(2):11 1981

The increasing incidence of pancreatic cancer, the growing environmental pollution problems, and our increased knowledge of interactions of various exogenous factors such as diet, sex, etc, heightens the need for information on etiology of pancreatic cancer. There are presently several models of carcinogen-induced cancer. Establishment of the capability of tissue to form active intermediates is necessary to establish a relationship between exposure to carcinogens and subsequent tumorigenic response. The present studies were undertaken to characterize the pancreatic metabolic system, specifically that which metabolizes the ubiquitous carcinogen, benzopyrene (BP). We determined the Km and Vmax of the BP hydroxylase enzyme reaction in male Sprague Dawley rats pretreated with 20 mg/kg 3-methylcholanthrene (3MC), 75 mg/kg phenobarbital (PB), or solvent as control. Type of cytochrome involved was examined by measuring the reaction in the presence of 7,8-benzoflavone (BF), an inhibitor of the cytochrome P-448-related enzyme activity. The data indicated that the enzyme activity was induced by pretreatment with PB but not with 3MC. These pretreatment protocols resulted in changes both in Km and Vmax. Studies with BF suggested that pancreatic tissue contained only one hemoprotein and point out species differences between the rat and guinea pig. These studies confirm the pancreatic capability to metabolize procarcinogens and to further degrade carcinogenic metabolites, and strengthens the role of carcinogen exposure in the etiology of pancreatic cancer. (no Refs)

69. THE INFLUENCE OF POLYCYCLIC AROMATIC HYDROCARBONS AS INDUCERS OF MONOOXYGENASES ON THE METABOLITE PROFILE OF BENZ(A)ANTHRACENE IN RAT LIVER MICROSOMES.

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Cancer Lett; 14(2):175-185 1981

Changes in metabolite profiles resulting from induction of monooxygenases by polycyclic aromatic hydrocarbons (PAH) in Wistar rats is reported. Benz(a)anthracene (BA) was used as substrate. Rat liver microsomes converted BA preferentially into 5,6-, 8,9-, and 10,11-trans-dihydrodiols. With control microsomes, approx 5x more 10,11-trans-dihydrodiol than 5,6-and 8,9-dihydrodiol was formed. All tested inducers increased the epoxidation at the 5,6-position and to a lesser extent at the 8,9-position. Oxidation at the 10,11-position, however, was decreased after almost all inducers. Treatment with more effective inducers resulted in an increased secondary metabolism, especially the formation of the bay-region dihydrodiol epoxide. While phenobarbital and the moderately-inducing PAH induced oxidation at the 5,6-and 8,9-positions, other compounds, especially the benzofluoranthenes, also induced oxidation at the 3,4-position. This reaction leads to formation of the ultimate carcinogen of BA, 3,4-dihydroxy-1,2-epoxy-1,2,3,4 tetrahydrobenz(a)anthracene. (35 Refs)

70. ENZYME INDUCTION AND HEPATIC GLYCEROLIPID SYNTHESIS IN RATS TREATED WITH 3-METHYLCHOLANTHRENE.

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Can J Biochem; 59(9):793-798 1981

Fasting male rats fed 3-methylcholanthrene in a daily dose of 40 mg/kg body wt-1 gave evidence of hepatic microsomal enzyme induction after 3 days through significantly increased hepatic aryl hydrocarbon hydroxylase activity, cytochrome P448 content, and characteristic changes in microsomal proteins analyzed by sodium dodecyl sulfate-polyacrylamide gel electrophoresis. Concomitantly, activities of aminopyrine N-demethylase and microsomal gamma-glutamyltransferase, which are increased in phenobarbital-treated rats, significantly declined. In contrast to phenobarbital, which has been previously shown to increase hepatic triacylglycerol content and in vitro glycerolipid synthesis, 3-methylcholanthrene did not affect hepatic triacylglycerol content, but did inhibit glycerolipid synthesis by cell-free preparations of rat liver and significantly reduced serum triacylglycerol concentration. Thus, the two prototypical drugs inducing characteristically different changes in microsomal enzyme and hemoprotein response also seem to differ in their effect upon another important microsomal function, hepatic glycerolipid synthesis. (Author abstract) (31 Refs)

71. IMIDAZOLE DERIVATIVES AS INHIBITORS OF CYTOCHROME P-450-DEPENDENT OXIDATION AND ACTIVATORS OF EPOXIDE HYDROLASF IN HEPATIC MICROSOMES FROM A MARINE FISH.

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Biochem Pharmacol; 30(20):2876-2880 1981

Binding of 4(5)-phenylimidazole, benzimidazole, and naptho(2,3,4',5')-imidazole to cytochrome P-450 in sheepshead hepatic microsomes was examined; effects of these compounds on benzo[a]pyrene metabolism in control and induced microsomes are described. (39 Refs)

ALTERATION OF OTHER CARCINOGEN-METABOLIZING ENZYMES BY CARCINOGENS

72. PULMONARY METABOLISM OF PROSTAGLANDINS E2 AND F2ALPHA BY HAMSTERS TREATED WITH BENZO(A)PYRENE (MEETING ABSTRACT).

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International Conference on Prostaglandins and Cancer, August 30-September 2, 1981, Washington, DC. Lombardi Cancer Center 75 pp., 1981.

Benzo(a)pyrene is a potent pulmonary carcinogen. We hypothesized that the chronic exposition of the lung to this toxic agent produces alteration of the prostaglandin metabolism. This was tested by studying the biotransformation of the prostaglandin E2 and prostaglandin F2 alpha by perfused isolated hamster lung. During 15 wk, one group of animals received an intratracheal administration of a suspension of benzo(a)pyrene (3 mg) adsorbed to charcoal in saline; a second group received a charcoal saline suspension whereas only saline was administered to the third group. Prostaglandins and their metabolites were separated by thin-layer chromatography and quantified by liquid scintillation. In all groups the prostaglandins E2 and F2 alpha were respectively metabolized at 65% and 40%. The main metabolites were the 13-14 dihydro-15-keto PGE2 and the 13-14 dihydro-15-keto PGF2 alpha. The other metabolites were the 15-keto PGE2 the 15-keto PGF2 alpha. About 10 to 15% of the PGE2 and 20 at 25% of the PGF2 alpha were found after a first passage through the lung. In hamsters treated for 15 wk, benzo(a)pyrene produced morphological alterations of the lung structure and increased the lung wt. However, our results suggest that the pulmonary metabolism of prostaglandins E2 and F2 alpha is not altered in these animals. (no Refs)

73. INDUCTION OF ORNITHINE DECARBOXYLASE IN CULTURED MAMMARY TUMOR CELLS (MEETING ABSTRACT).

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In Vitro; 17(3):242 1981

At present, little is known concerning the role played by polyamines in mammary cancer. Since in vivo studies are difficult to interpret at the cellular level, we have developed a defined in vitro system consisting of neoplastic epithelial cells derived from an N-nitrosomethylurea induced rat mamm ary adenocarcinoma. Ornithine decarboxylase (ODC), the rate-limiting step in polyamine synthesis, was measured in these cells by the in situ method of Patterson and Maxwell. To induce ODC, late log-phase cells were grown in serum-depleted medium. The kinetics of ODC induction was similar to that reported in other cell lines. Specific activity (sp act) at 0, 15 and 60 min was less than 0.5, 3.25 and 6.30 nmoles carbon dioxide/mg prot/hr, respectively; between 1 and 2 hr little change in sp act was observed. The specificity of the reaction was assessed by addition of inhibitors of the reaction mixture for the 2 hr assay period. There was an absolute requirement for pyridoxal phosphate; the reaction product, putrescine, inhibited ODC in a logarithmic fashion, and the competitive inhibitor alpha-methylornithine reduced enzyme activity by half. (1 Ref)

74. TUMOR PROMOTION AND PROSTAGLANDINS (MEETING ABSTRACT).

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International Conference on Prostaglandins and Cancer, August 30-September 2, 1981, Washington, DC. Lombardi Cancer Center 75 pp., 1981.

The tumor promotors 12-O-tetradecanoylphorbol-13-acetate (TPA) and phenobarbital both appear us to induce the activity of rat hepatic ornithine decarboxylase (ODC). This induction is dose dependent, with an optimum dose at 20 ug -0.1 mg TPA per kg body wt and at 100 mg phenobarbital per kg body wt. The ODC activity has a maximal value at 4 hr after ip injection of the tumor promotor. It further is protein- and RNA-synthesis dependent. Treatment with retinyl-acetate one hr prior to TPA results in a dose dependent inhibition, being 85% at 20 mg per kg body wt, of the induce ODC activity. Retinyl-acetate at this dose fails to inhibit the phenobarbital induced activity. Analogical pretreatment with indomethacin shows an inhibition of the induced ODC activity, which raises the suggestion of the involvement of prostaglandins in the sequence of events from the application of the tumor promotor to the increase in activity of rat hepatic ornithine decarboxylase. Ip application of prostaglandins (PG E2 and PG F2alpha) both appear to inhibit ODC activity. These two observations possibly suggest a difference in mode of action between intra- and extracellular prostaglandins. (no Refs)

75. EFFECTS OF VARIOUS CHEMICALS INCLUDING BILE ACIDS AND CHEMICAL CARCINOGENS ON THE INHIBITION OF METABOLIC COOPERATION.

Noda K, Umeda M, Ono T
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Gan; 72(5):772-776 1981

The effects of various chemicals, such as bile acids, a lectin, polyamines, and chemical carcinogens, on metabolic cooperation in the hypoxanthine-guanine phosphoribosyl transferase system were surveyed. Among bile acids, lithocholic acid, chenodeoxycholic acid and ursodeoxycholic acid inhibited metabolic cooperation. However, cholic acid, deoxycholic acid and dehydrocholic acid did not. There was a structure-activity relationship among these compounds for the inhibition of metabolic cooperation. The metabolic cooperation was not inhibited by such chemicals as phytohemagglutinin, three polyamines, 7,12-dimethylbenz[a]anthracene, N-methyl-N'-nitro-N-nitrosoguanidine, 4-nitroquinoline 1-oxide and three biphenyl compounds. These results should be useful in relation to studies on the mechanism of inhibition of metabolic cooperation and on the relationship between this inhibitory activity and the tumor-promoting activity of various chemicals. (Author abstract) (12 Refs)

BIOASSAY BASED UPON ACTIVATION

76. APPLICATION TO BENZO(A)PYRENE FED RATS OF A PROPOSED SHORT-TERM IN VIVO CARCINOGEN SCREENING PROTOCOL (MEETING ABSTRACT).

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Toxicologist; 1(1):36 1981

This study was undertaken to determine if induction of presumptive pre-cancerous lesions by benzo(a)pyrene (BP) could be predicted in a short-term treatment by demonstration of urinary mutagenesis and by increased concentration in the blood of the oncodevelopmental protein alpha fetoprotein (AFP). Existence of pre-cancerous lesions was confirmed by gamma glutamyl transpeptidase staining of liver sections from treated animals. Male weanling F344 Schf rats were fed semi-purified diets containing 0, 1, 100 or 1000 ppm BP with or without 0.05% sodium phenobarbital for six to thirteen wk. Blood was obtained at one to two wk intervals by cardiac puncture and plasma AFP levels were determined by sandwich type radioimmunoassay. Urine was collected for eight hr during the sixth wk of treatment. Glucuronidase-treated specimens were tested for mutagenesis in salmonella typhimurium strains TA98 and TA100 with and without microsomal activation. Liver specimens were stained for gamma glutamyl transpeptidase (GGT) activity and examined for presence of foci of altered cells. Those treatments resulting in elevated plasma AFP and mutagenic urine were associated with development of GGT-positive hepatic cell foci. This protocol could be applied early in the range finding phase of a carcinogenesis bio-assay to aid in selection of substances for long-term testing. (no Refs)

77. EVALUATION OF TRANSFORMATION ASSAYS USING C3H 10T1/2 CELLS FOR USE IN SCREENING (MEETING ABSTRACT).

Schechtman LM, Lubet RA, Kouri RE, Sivak A, Tu AS
Microbiological Associates, Bethesda, MD, 20816
Second Annual NCI/EPA/NIOSH Collaborative Workshop: Progress on Joint Environmental and Occupational Cancer Studies, September 9-11, 1981, Rockville, Maryland. National Cancer Institute 33 pp., 1981.

The C3H 10T 1/2 C1 8 (10 T 1/2) cell transformation system is being evaluated independently and simultaneously in two laboratories for its utility, reliability and reproducibility as a predictive in vitro screening test for potential chemical carcinogens. Eleven known chemicals were tested using a standard protocol in the absence of exogenous metabolic activation. The polycyclic hydrocarbon carcinogens 3-methylcholanthrene, 7,12-dimethylbenz(a)anthracene, benzo(a)pyrene (BaP) and dibenz(a,h)anthracene induced Type II and Type III foci, while the non-carcinogens phenanthrene and anthracene were non-transforming. The direct-acting agents N-methyl-N'-nitro-N-nitrosoguanidine (MNNG), ethyl methanesulfonate and N-acetoxy-2-fluorenylacetamide (AFAA) induced little or no transformation. The procarcinogenic aromatic amines N-2-fluorenylacetamide and 2-anthramine were not active. Thus the 'standard' assay shows a range of sensitivity, depending upon the specific class of chemicals employed. To overcome such limitations, the assay has been modified by (a) cell synchronization, (b) increasing cells at risk, (c) replating treated cells ('level II transformation'), and (d) supplying exogenous metabolizing activity (eg hepatocytes, S-9). Transformation of 10T 1/2 cells was induced by MNNG and AFAA using modified protocols without a metabolic supplement. Use of an Aroclor-1254-induced rat hepatic S-9 resulted in activation of a variety of chemicals to cytotoxic metabolites. S-9-mediated enhancement of phenotypic transformation has been thus far achieved with BaP. Additional studies employing hepatocytes for metabolic activation are in progress. Validation studies of cell populations derived from Type III foci showed that while most transformed populations grew in soft agarose, their tumorigenic potential was dependent on the strain, age and immunosuppression of host animals used. Efforts are ongoing to assess the efficacy of these different approaches in rendering the 10T 1/2 cell system responsive to diverse classes of procarcinogens and direct-acting carcinogens. Validation of the transformation system is being carried out by testing coded samples. (no Refs)

78. MORPHOLOGIC ANALYSIS OF ATYPICAL ACINAR CELL LESIONS (AACL) INDUCED IN RAT PANCREAS BY 4-HYDROXYAMINOQUINOLINE-1-OXIDE (4-HAQO) (MEETING ABSTRACT).

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Department of Pathology and Cancer Center, Northwestern University Medical School, 303 E. Chicago Avenue, Chicago, IL, 60611
Newsletter Natl Pancreas Cancer Project; VI(2):48 1981

A metabolite and possible proximate carcinogen of 4-nitroquinoline-1-oxide, 4-HAQO, is both toxic and carcinogenic for pancreas. A single IV injection of 4-HAQO in male Wistar rats at a dose of 6 mg/kg body wt induced AACL in 100% of the animals. AACL could be classified histologically as zymogen-poor and zymogen-rich foci, and zymogen-rich nodules (grossly visible). The zymogen-poor foci contained between 20-300 cells and rarely more than 500 cells. Cells in such foci were large, contained a large irregular nucleus with a prominent nucleolus, and a markedly basophilic cytoplasm with a few to small numbers of zymogen granules. By transmission electron microscopy (TEM) these cells showed markedly irregular lateral plasma membranes, a well developed rough endoplasmic reticulum (RER) and a few zymogen granules. Cells in zymogen-rich foci and nodules were arranged in acini which were larger than adjacent acini. The cells contained an intensely eosinophilic granular cytoplasm, and a large oval basophilic nucleus with a prominent nucleolus. By TEM, the cells showed a zymogen rich cytoplasm, RER and irregular lateral membranes. The mitotic and [3H] thymidine labeling indices respectively of both cell variants of AACL were as follows: eosinophilic cells, 2.75 and 23.2 basophilic cells 0.125 and 1.2 as compared to 0 and 1 for normal pancreatic acinar cells. These studies indicate that 4-HAQO induces at least 2 varients of AACL with different morphological features and growth potential. Their role in the pathogenesis of acinar cell adenomas and carcinomas remains to be elucidated. (no Refs)

79. USE OF CULTURED MAMMALIAN CELL TECHNIQUES TO EVALUATE THE TOXICITY OF CHEMICALS TRANSFORMED IN LABORATORY TERRESTRIAL ECOSYSTEMS (MEETING ABSTRACT).

Ross WD, Wininger MT, Hillan WJ
Monsanto Research Corporation, 1515 Nicolas Road, Dayton, OH, 45418
In Vitro; 17(3):224 1981

Mammalian cell culture techniques have been used to assess the acute cytotoxicity and potential health hazards of degradation products and metabolites resulting from the transformation of chemicals applied to or spilled on soil. Laboratory ecosystems, containing intact 10 cm x 70 cm soil cores have been designed for sampling leachates at 10-cm depth intervals along the vertical soil core. Stainless steel probes are inserted laterally into the soil and sampling boats containing adsorbents are positioned in the probes to recover organic compounds resulting from the transformation of test compounds applied at the soil core surface. Openings in the probes and sampling boats permit leachate containing the products to flow through. Three mammalian cell test methods were evaluated for determining acute cytotoxicity: (a) direct application of the adsorbent to an agar overlay culture containing D98S human and CHO-K1 cells; (b) application of a dimethylsulfoxide (DMSO) extract of the adsorbent to a mammalian cell clonal assay technique; and (c) bioautographic techniques in which thin-layer chromatography (TLC) of the soil leachates were applied to mammalian cell agar overlay culture plates. Bioactive spots indicating toxicity were detected by noting the slowing of growth or the death of the underlying cells. (no Refs)

REVIEWS AND OTHER RELEVANT STUDIES

80. ADVANCES IN THE METABOLIC ACTIVATION OF CARCINOGENS.

Ivanetich KM
Dept. Medical Biochemistry, Univ. Cape Town Medical Sch., Observatory, Cape Province, South Africa
S Afr Cancer Bull; 25(1/2):105-116 1981

Of the known chemical carcinogens, an ever-increasing number require metabolic activation to elicit their mutagenic and carcinogenic effects. In a review, it is noted that the enzymes known as cytochrome P-450 alone or in conjunction with other enzymes are involved in this activation. The activated metabolites may initiate carcinogenesis by covalently binding to selected sites on nuclear DNA in somatic cells. Detailed pathways are presented for a number of carcinogens, such as chlorinated ethylenes, aflatoxin B1, acetylaminofluorene and benzpyrene. (22 Refs)

81. EPOXIDE HYDROLASE AND HEPATOCARCINOGENESIS.

Griffin MJ
Oklahoma Medical Res. Foundation, 825 N.E. 13th St., Oklahoma City, OK, 73104
Trends Pharmacol Sci; 2(10):257-258 1981

The role of epoxide hydrolase (EH) in hepatocarcinogenesis is described. A search for markers associated with multistage development of preneoplastic cells through focal and nodular stages to a hepatoma led to the discovery of the preneoplastic (PN) antigen, a microsomal antigen present in nodule and hepatoma cells. Through immunological studies EH was found to be a major PN antigen. A class of heterocyclics, including isoquinoline, norharman, and ellipticine, has been shown to stimulate microsomal EH. The requirement for a pyridinic nitrogen beta to a ring fusion suggests enzyme dictated specificity, while the pyridinic nitrogen suggests an electrophilic target. Reactive electrophiles, such as epoxides, have been found to regulate cell function and development. Perhaps endogenously formed epoxides play a role in liver adaptation during hepatocarcinogenesis. All hepatocarcinogen tests seem to cause an early (1-5 wk) induction of EH activity and microsomal content of the enzyme protein. One explanation for this early induction of EH is the production of increased amounts of an endogenous epoxide as an acute response. EH regulation during hepatocarcinogenesis is discussed with 2-acetylaminofluorene hepatocarcinogenesis as an example. (12 Refs)

82. STRUCTURAL ASPECTS OF CHEMICAL CARCINOGENESIS (MEETING ABSTRACT).

Glusker JP
Institute for Cancer Research, 7701 Burholme Avenue, Philadelphia, PA, 19111
Molecular Structure and Biological Activity: A Symposium on Biologically Active Molecules, (Twelfth Congress), August 26-28, 1981, Buffalo, New York. International Union of Crystallography 89 pp., 1981.

The process of carcinogenesis by polycyclic aromatic hydrocarbons (PAH) involves the enzymatic 'activation' of the hydrocarbon to a diol epoxide and, it is presently believed, alkylation of DNA by this alkylating agent. The shape and size of the PAH is important. If it is too large or too small it is not as potent a carcinogen. The optimal size approaches that of a steroid or a base pair. This shape may also have significance in the interaction of the PAH with the hydroxylating enzyme. In addition, methyl substitution for hydrogen in the 'bay area' of a PAH, which characteristically causes distortions as a result of steric effects, often enhances carcinogenic activity. Studies in several systems have led to the conclusion that flatness is not a criterion for carcinogenicity and that total intercalation of the hydrocarbon cannot occur. The benzoflavone that inhibits the 'activation' process has been shown by x-ray studies to be nonplanar. Interactions between hydroxyl and epoxide groups in the same molecule may affect reactivity. The immediate aim of these studies is to determine what effects alkylation by an activated PAH can have on DNA. The structure of a nucleoside alkylated by chloromethyl PAH has been studied and it is shown, as predicted, that the base and PAH portion lie almost perpendicular to each other. Some possible effects of such alkylation on DNA structure will be discussed. (no Refs)

83. THE NATURE OF THE RESISTANCE TO CYTOTOXICITY INDUCED IN HEPATOCYTES BY FEEDING A CARCINOGENIC REGIME OF AFLATOXIN B1 TO MALE FISCHER RATS (MEETING ABSTRACT).

Neal GE, Cabral JR
Toxicology Unit, Medical Research Council Laboratories, Woodmansterne Road, Carshalton, Surrey, SM5 4EF, England
Toxicologist; 1(1):34 1981

Evidence is emerging that in the case of hepatocarcinogenesis by low-level administration of many different carcinogens, the irreversible carcinogenic change takes place at a time when the level of presumptive mutagenic lesions in the hepatic DNA is very much lower than that present following subcarcinogenic dosing. Aflatoxin B1 action clearly demonstrates this effect. It has been suggested that the mechanism is an enhanced repair of mutagenic lesions, but the kinetics of DNA binding of labelled aflatoxin are incompatible with this theory. Reduced binding of aflatoxin appears prinicipally to be due to enhanced detoxification of the activated toxin, and this has been demonstrated in vitro binding experiments. Induction of high levels of reduced glutathione and probably S-transferase enzymes appears to be responsible for the effect. These changes are principally, if not exclusively, located in foci of gamma glutamyl transferase positive cells. Evidence for the significance of these changes in terms of induction of preneoplastic lesions will be presented. (no Refs)

84. TOXICOLOGICAL CONSIDERATIONS FOR THE MEDICINAL CHEMIST.

Finch N
Pharmaceuticals Div., CIBA-Geigy Corporation, Summit, NJ, 07901
Med Res Rev; 1(4):337-372 1981

Toxicological considerations in the development of new drugs are reviewed. Expanding knowledge of drug metabolism and toxicology allows better direction of research into those compounds having the best chance of passing biological tests. One apparent mechanism of chemical carcinogenesis is attack by electrophilic molecules on DNA, nuclear proteins, or other cell components. A second mechanism is the induction of enzyme systems, particularly cytochrome P450 by a compound or its metabolites. Other toxicological problems include phospholipidosis, blood dyscrasias, effects on liver function, dermatological problems, hearing loss, and lupus syndrome. All of these should be considered in proposing new drugs for testing. A drug should have sufficient reversible toxicity to produce the desired effect without producing permanent damage to the patient. Quantitative structure-activity relationships and empirical approaches are reviewed. Structure-toxicity relationships of specific compounds are presented. In vivo transformation of drugs is discussed. (117 Refs)

85. MUTAGENESIS BY CHEMICAL AGENTS IN V79 CHINESE HAMSTER CELLS: A REVIEW AND ANALYSIS OF THE LITERATURE.

Bradley MO, Bhuyan B, Francis MC, Langenbach R, Peterson A, Huberman E
Merck Inst. for Therapeutic Res., West Point, PA, 19486
Mutat Res; 87(2):81-142 1981

The current literature on chemically induced specific locus mutations in the V79 Chinese hamster cell line are reviewed and evaluated. Characteristics of V79 cells, various genetic markers, and protocols for mutant induction by chemicals in the presence and absence of activation systems are described. The chemicals which were tested in V79 cells for mutagenic activity are listed. The usefulness of V79 cells for the screening of environmental chemicals which may be hazardous to humans is evaluated. Mutagenesis assays are discussed in relation to characteristics of the V79 cell line, genetic markers (hypoxanthine-guanine phosphoribosyl transferase [HGPRT] locus, reversion of HGPRT- mutants, ouabain-resistance, drug resistance, and auxotrophic, prototrophic and temperature-sensitive mutants) of V79 cells, and suggested and testing (toxicity and dose selection, standard mutagen treatment conditions, expression time, mutant selection, identification of phenotypic variants as presumptive genotypic variants, metabolic activation, cell-mediated mutagenesis, tissue homogenate-mediated mutagenesis, positive and negative controls, experimental design) protocols. Test performance is evaluated based on an analysis of the literature. The strengths and weaknesses of the V79 assay are considered. The role of the assay in mutagenicity and carcinogenicity testing programs is discussed. (162 Refs)

86. MAMMALIAN IN VIVO AND IN VITRO CYTOGENETIC ASSAYS: A REPORT OF THE U.S. EPA'S GE NE-TOX PROGRAM.

Preston RJ, Au W, Bender MA, Brewen JG, Carrano AV, Heddle JA, McFee AF, Wolff S, Wassom JS
Biology Div., Oak Ridge Natl. Lab., Oak Ridge, TN, 37830
Mutat Res; 87(2):143-188 1981

An assessment made by the United States Environmental Protection Agency Gene-Tox Program's Work Group on Mammalian cytogenetics of the clastogenic effects of chemicals in in vivo and in vitro mammalian assays based on 177 papers is presented. General considerations used in the interpretation of data included differential sensitivity of cells in different stages of the cell cycle, metabolic activation, suitability of protocols, and tabular presentation of data base. The protocols for testing and the chemicals reviewed for the bone marrow, spermatogonia, spermatocyte (treated spermatogonial stem cells and treated spermatocytes), oocytes and early embryo, in vitro cell culture assay, and peripheral leukocyte or lymphocyte assays are presented. Advantages and disadvantages of the cytogenetic assay systems are considered. (162 Refs)

87. SECOND ANNUAL REPORT ON NATIONAL CANCER INSTITUTE AND ENVIRONMENTAL PROTECTION AGENCY PROJECTS.

Department of Health and Human Services
Public Health Service, NIH, Bethesda, MD
Second Annual Report on National Cancer Institute and Environmental Protection Agency Projects. Bethesda, MD, National Cancer Institute, 384 pp., 1981.

Current projects underway under the auspices of the National Cancer Institute and the Environmental Protection Agency are described. Progress reports are presented for the following: a data base for chemicals identified in human biological media; in vivo analysis of UV-B-induced photooxidations; use of the hairless mice for carcinogenesis studies; chronic toxicity and carcinogenicity to rats and mice of chloroform in drinking water; the effects of carcinogens, mutagens, and teratogens on non-human (aquatic) species; the cost effectiveness of two types of personal UV-B dosimeters; the effects of varying doses of UV on mammalian skin; immunodiagnostic markers for breast cancer; antigens on human lymphoid organs for the immunodiagnosis of leukemias and lymphomas; human epithelial cell metabolic activation systems for use with human cell mutagenesis; evaluation of the transformation assay using C3H 10T1/2 cells for use in screening chemicals for carcinogenic potential; national mortality data bases for environmental epidemiology; epidemiologic field studies on ecological relationships between specified toxic substances and cancer morbidity and mortality; an epidemiologic study of populations in Turkey previously exposed to hexachlorobenzene; a case control study of lung, pancreas, and stomach cancer in Southern Louisiana; support services for epidemiologic studies of lung cancer in communities with non-ferrous smelters; an epidemiologic study of the i ncidence of cancer as related to industrial emissions in the heavily industrialized parts of Contra Costa County in California; an environmental data base for New Jersey to be used in epidemiological studies; an etiologic study of respiratory cancer in coastal Texas; and completion of the NCI/NCHS cooperative study of 1972 mortality data. (no Refs)

88. AIR POLLUTION AND BIOLOGICAL DEFENCE.

Schlipkoter HW, Dolgner R
Med. Institut fur Umwelthygiene an der Univ., Gurlittstrasse 53, D-4000 Dusseldorf 1, W. Germany
Zentralbl Bakteriol [Orig A]; 172(4/5):299-311 1981

A review is presented of the effects of air pollution on defense mechanisms of the body which may in turn account for differences in individual reactivity to such pollution. Some important findings relating to this problem follow: deterioration of lung clearance after inhalation of NO2 and lead chloride; damage to alveolar macrophages by air-borne particulates in vitro and in vivo; enhanced activation of C3 complement fraction under the influence of air pollutants; higher frequency of enlarged tonsils and lymph nodes, of pathogenic bacteria on tonsillar surfaces, and of relatively lower lysozyme concentrations in children living in urban or industrialized areas; decreased resistance to infections related to inhalation of O3 or a lead aerosol; immuno-suppressive effect of heavy metals and organic compounds; allergic reactions to many chemicals; detoxification and toxification, eg formation of ultimate carcinogens, and of organic molecules; induction or inhibition of benzo(a)pyrene metabolism by particulate extracts or by CO, NO2, and lead; deficiency of DNA-repair in disease conditions predisposing to development of cancer; tendency, in allergic subjects, to a relatively lower incidence of cancer; adaptation to the effect of CO and SO2. These facts, and others not cited, support a close connection between various defense mechanism, air pollution, and its effects on the human organism. (55 Refs) (In GER)

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1. NUTRITION AND ENVIRONMENTAL HEALTH: THE INFLUENCE OF NUTRITIONAL STATUS ON POLLUTANT TOXICITY AND CARCINOGENICITY. VOLUME 2: MINERALS AND MACRONUTRIENTS.

Calabrese EJ

Environmental Health Program, Div. Public Health, Univ. Massachusetts, Amherst, MA

Nutrition and Environmental Health: The Influence of Nutritional Status on Pollutant Toxicity and Carcinogenicity. Volume 2: Minerals and Macronutrients. New York, John Wiley and Sons, 468 pp., 1981.

EPIDEMIOLOGY, ETIOLOGY AND GENETIC ASPECTS OF HUMAN CANCER

2. RETROSPECT AND PROSPECT OF STUDIES ON DIGESTIVE SYSTEM DISEASES IN CHINA.

Zhang X

Dept. Internal Medicine, Capital Hosp., Chinese Acad. Medical Sciences, Beijing, People's Republic of China

Zhonghua Xiaohua Zazhi; 1(1):1-4 1981

In CHI

3. EPIDEMIOLOGY OF PITUITARY ADENOMAS.

Gold EB

Dept. Epidemiology, Sch. Hygiene and Public Health, Johns Hopkins Univ., 615 Wolfe St., Baltimore, MD, 21205

Epidemiol Rev; 3:163-183 1981

4. BLADDER CANCER EPIDEMIOLOGY.

Matanoski GM, Elliott EA

Dept. Epidemiology, Sch. Hygiene and Public Health, Johns Hopkins Univ., 615 North Wolfe St., Baltimore, MD, 21205

Epidemiol Rev; 3:203-229 1981

5. THE EPIDEMIOLOGY OF BENIGN BREAST DISEASE.

Ernster VL

Dept. Epidemiology and International Health, 1699HSW, Univ. California, San Francisco, CA, 94143

Epidemiol Rev; 3:184-202 1981

ENVIRONMENTAL AND OCCUPATIONAL FACTORS IN CARCINOGENESIS

6. AIR POLLUTION AND BIOLOGICAL DEFENCE.

Schlipkoter HW, Dolgner R

Med. Institut fur Umwelthygiene an der Univ., Gurlittstrasse 53, D-4000 Dusseldorf 1, W. Germany

Zentralbl Bakteriol [Orig A]; 172(4/5):299-311 1981

In GER

7. CANCER AND THE PHYSICOCHEMICAL QUALITY OF DRINKING WATER IN QUEBEC.

Thouez JP, Beauchamp Y, Simard A

Dept. Geography, Univ. Montreal, Montreal, Quebec, Canada

Soc Sci Med [Med Geogr]; 15(1):213-223 1981

VIRAL AND IMMUNOLOGICAL ASPECTS OF CARCINOGENESIS

8. ONCOGENIC VIRUSES.

Wyke JA

Imperial Cancer Res. Fund, P.O. Box 123, Lincoln's Inn Fields, London WC2A 3PX, England

J Pathol; 135(1):39-85 1981

9. ROLE OF VIRUSES IN THE ETIOLOGY OF NATURALLY OCCURRING FELINE LEUKEMIA.

Essex M, Grant CK, Cotter SM, Hardy Jr WD

Dept. Microbiology, Harvard Sch. Public Health, 665 Huntington Ave., Boston, MA, 02115

Haematol Blood Transfus; 26:483-487 1981

METHODOLOGY IN CARCINOGENESIS RESEARCH

10. MAMMALIAN IN VIVO AND IN VITRO CYTOGENETIC ASAYS: A REPORT OF THE U.S. EPA'S GEN E-TOX PROGRAM.

Preston RJ, Au W, Bender MA, Brewen JG, Carrano AV, Heddle JA, McFee AF, Wolff S, Wassom JS

Biology Div., Oak Ridge Natl. Lab., Oak Ridge, TN, 37830

Mutat Res; 87(2):143-188 1981

11. BACTERIAL SYSTEMS FOR CARCINOGENICITY TESTING.

Mohn GR

Dept. Radiation Genetics and Chemical Mutagenesis, State Univ. Leiden, Wassenaarseweg 72, 2333 AL Leiden, The Netherlands

Mutat Res; 87(2):191-210 1981

12. MUTAGENESIS BY CHEMICAL AGENTS IN V79 CHINESE HAMSTER CELLS: A REVIEW AND ANALYSIS OF THE LITERATURE.

Bradley MO, Bhuyan B, Francis MC, Langenbach R, Peterson A, Huberman E

Merck Inst. for Therapeutic Res., West Point, PA, 19486

Mutat Res; 87(2):81-142 1981

OTHER REVIEWS IN CARCINOGENESIS

13. CANCER BIOLOGY.

Ruddon RW

Biological Markers Program, NCI-Frederick Cancer Res. Center, Frederick, MD

Cancer Biology. New York, Oxford University Press, 344 pp., 1981.

14. AVOIDABLE CANCER: ATTRIBUTION OF RISK.

Doll R

Radcliffe Infirmary, Oxford, England

S Afr Cancer Bull; 25(3):125-146 1981

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Activation and Metabolism of Carcinogens

SERIES CK08 No. 82/04

APRIL, 1982

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service • National Institutes of Health • National Cancer Institute

HE 20. 3173/2:

METABOLIC ACTIVATION OF CARCINOGENS

1. STUDIES ON THE MECHANISM OF CARCINOGENICITY OF DIETHYLSTILBESTROL: ROLE OF METABOLIC ACTIVATION.

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Food Cosmet Toxicol; 19(5):611-615 1981

Oxidative metabolism of diethylstilbestrol (DES), meso-hexestrol (HES), and E,E-dienestrol (E,E-DIES) is reviewed. DES is metabolized to a variety of oxidative metabolites along several pathways involving reactive intermediates. This observation, together with evidence that DES also produces genetic damage, raises the possibility that metabolic activation may be involved in DES carcinogenicity. The mechanism for organ-specific carcinogenicity of DES may involve formation of reactive metabolites that retain their estrogenicity and are thus accumulated in estrogen target organs. A second possibility may involve the preferential formation of reactive metabolites in target organs by specific metabolites. Metabolic oxidation of HES is confined to the aromatic and aliphatic portions of the molecule. E,E-DIES is oxidized at the aromatic ring and at the olefinic double bond, and there is no indication of aliphatic hydroxylation. These analogues may be useful for further clarifying the role of metabolic activation in the genetic toxicity and carcinogenicity of DES. (34 Refs)

2. THE ACTIVATION OF AFLATOXIN B1 IN LIVER SLICES AND IN BACTERIAL MUTAGENICITY ASSAYS USING LIVERS FROM DIFFERENT SPECIES INCLUDING MAN.

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Carcinogenesis; 2(10):1063-1068 1981

Activation of aflatoxin B1 (AFB1) was compared in two in vitro systems: binding to DNA in liver slices incubated with 14C- or 3H-AFB1 and in standard bacterial mutation systems using 9000 x gravity supernatant (S-9) fractions from uninduced livers for activation. The results were compared in several rodent species in an effort to correlate them with known trends in carcinogenicity. Covalent binding of 14C-AFB1 to DNA from liver slices showed the order rat greater than hamster greater than mouse. Phenobarbitone pretreatment of rats decreased binding, and binding of aflatoxin G1 (AFG1) was less than that of AFB1. These findings all were correlated with relative susceptibility to AFB1-induced hepatocarcinogenesis. An exception to this trend was the similar level of binding found in male and female rat livers. Levels of 3H-AFB1 binding to DNA in human liver biopsies ranged from 0.7-8.5 nanog AFB1/mg DNA, which was similar to the range seen in the mouse and hamster. Mutagenicity data did not correlate with carcinogenicity in relation to species differences, as the efficiencies of livers from the three species for activating AFB1 mutagenicity were hamster greater than rat greater than mouse. AFG1 mutagenicity generally was markedly less than that of AFB1 when activated by rat liver S-9. The correlation between AFB1 binding to DNA in liver slices in various rodent species and susceptibility to AFB1 hepatocarcinogenesis and its modification in the rat by phenobarbitone suggests that these differences are related to differences in metabolic activation of AFB1 to its reactive species, its subsequent detoxification, and macromolecular interaction. (30 Refs)

3. METABOLIC ACTIVATION OF AFLATOXIN B1 BY LIVER TISSUE FROM MALE FISCHER F344 RATS OF VARIOUS AGES.

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Dept. Biological Sciences, Illinois State Univ., Normal, IL, 61761
Mech Ageing Dev; 17(2):163-171 1981

The effect of aging on the ability of the liver to activate chemical procarcinogens was studied using 12-, 18-, and 27-mo-old male Fischer F344 rats. The cytochrome P-450 content of the S9 and microsomal fractions of the liver decreased approx 30% between 12 and 18 mo of age. The structural conformation of cytochrome P-450 in microsomes from 12-, 18-, and 27-mo-old rats was studied using electron-spin resonance spectroscopy. An age-related decrease in the amount of cytochrome P-450 ferric iron in the liver microsomes was observed. The conversion of the chemical procarcinogen aflatoxin B1 to mutagenic compounds by the S9 and microsomal fractions of liver was measured using the Salmonella typhimurium bioassay. A 40-50% decrease in the metabolic activation of aflatoxin B1 was observed between 12 and 18 mo of age. However, the activation of aflatoxin B1 did not change after 18 mo of age. The age-related decrease in the activation of aflatoxin B1 by liver appears to be due to a decrease in the metabolic activity of the mixed-function oxidase system. (Author abstract) (27 Refs)

4. SPECIFICITY OF RABBIT PULMONARY CYTOCHROME P-450 ISOZYMES IN THE ACTIVATION OF SEVERAL AROMATIC AMINES AND AFLATOXIN B1.

Robertson IG, Philpot RM, Zeiger E, Wolf CR
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Mol Pharmacol; 20(3):662-668 1981

The activation of 2-aminoanthracene (2-AA), 2-aminofluorene (2-AF), 2-acetylaminofluorene (2-AAF), and aflatoxin B1 (AFB1) by rabbit pulmonary and hepatic preparations was studied using the Salmonella strain TA98. In experiments with either antibodies to specific cytochrome P-450 isozymes or monooxygenase systems reconstituted from purified enzymes, the observed activities were related to the relative concentrations and activities of these isozymes. Rabbit pulmonary and hepatic S16 fractions produced mutagenic products from 2AA, 2AAF, and 2AF, and AFB1. The hepatic fraction was more active, with regard to the amount of S16 protein required to produce a given number of revertants, with 2AA (up to 2x), 2-AAF (2.5-5x), and AFB1 (5x), whereas the pulmonary fraction was more active with 2AF (up to 2x). On the basis of cytochrome P-450 content, the activity of the pulmonary fraction was greater than or equal to that of the hepatic fraction. For a given substrate concentration, a comparison of the amounts of cytochrome P-450 required for equivalent activity showed that the pulmonary microsomal fraction was 3-4, 20-25, and 25-30x more active than the hepatic fraction in the formation of mutagenic products from 2AAF, 2AA, and 2AF, respectively. With AFB1, similar activities were obtained with both microsomal fractions, the pulmonary fraction being slightly more active. The promutagens 2AA, 2AF, and 2AAF were substrates for both P-450II and P-450LM4 but were inactive with P-450I. P-450LM1 showed greater activity with 2AAF, however, P-450II gave 10-20 times more mutagenic activity with 2AA and 2AF than did P450LM4. With AFB1, only incubations containing P-450I gave a significant increase in the number of revertants. Experiments with antibodies against P-450I and P-450II confirmed these findings. (29 Refs)

5. INTERTISSUE VARIATION IN BENZO(A)PYRENE METABOLISM BY HUMAN SKIN, LUNG AND LIVER IN VITRO.

Milo GE, Trewyn RW, Tejwani R, Oldham JW, Douglas WH
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Sci Tech Aerosp Rep; 19(18):2533 1981

An environmental carcinogen, benzo(a)pyrene (B(a)P), is shown to transform human skin fibroblasts in vitro. This fossil fuel combustion product and other polynuclear hydrocarbons have exhibited a requirement to be biotransformed to their ultimate carcinogenic forms to induce transformation. B(a)P diolepoxides are the most cited candidates as ultimate carcinogens. Results suggest that either the ultimate form of the carcinogen is different for fibroblasts and epithelial cells or the quantitative generation of hydroxylated metabolites is not required for neoplastic transformation in fibroblast cells. If hydroxylation is required, then the site of hydroxylation may be the significant factor. Present evidence suggests that in B(a)P treated fibroblasts the activation of B(a)P in the cell takes place other than the microsomal P450 complex, presumably in the nucleus. (Author abstract) (no Refs)

6. EFFECTS OF FLUORINE SUBSTITUTION ON THE TUMOR INITIATING ACTIVITY AND METABOLISM OF 5-HYDROXYMETHYLCHRYSENE, A TUMORIGENIC METABOLITE OF 5-METHYLCHRYSENE.

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Div. Chemical Carcinogenesis, Naylor Dana Inst. for Disease Prevention, American Health Foundation, Valhalla, NY, 10595
Carcinogenesis; 2(10):1027-1032 1981

Tumor-initiating activity of 5-methylchrysene (5-MeC) on mouse skin was compared with that of a major 5-MeC metabolite, 5-hydroxymethylchrysene (5-HOMeC). After an initiating dose of 30 ug, with promotion by tetradecanoylphorbol acetate, 5-HOMeC induced skin tumors in 90%, with 9.5 tumors/mouse. 5-MeC resulted in 75% incidence of skin tumors with 6.2 tumors/mouse. The tumorigenic activities after a 10 ug initiating dose were: 5-HOMeC, 45% incidence and 2.6 tumors/mouse; 5-MeC, 55% incidence and 5.6 tumors/mouse. The compound 6,hydroxymethylchrysene was inactive. The tumor initiating activities of two monofluoro derivatives also were investigated to elucidate the mechanism of 5-HOMeC activation. 7-Fluoro-5-hydroxymethylchrysene (7-F-5-HOMeC) was as tumorigenic as 5-HOMeC, whereas 3-fluoro-5-hydroxymethylchrysene (3-F-5-HOMeC) was significantly less tumorigenic. The inhibition of tumorigenicity by substitution of fluorine at the 3-position, but not the 7-position of 5-HOMeC is analogous to previously described results with 5-MeC and suggests a similar mechanism of activation for both compounds. Metabolites formed upon incubation of 5-HOMeC with cofactors and the 9,000x gravity supernatant from Aroclor pretreated rats were separated by high pressure liquid chromatography. The 1,2-dihydrodiol and 7,8-dihydrodiol of 5-HOMeC were identified. The major phenolic metabolite was 1-hydroxy-5-hydroxymethylchrysene. In the in vitro metabolism of 7-F-5-HOMeC under the same conditions, 1,2-dihydrodiol was identified but not 7,8-dihydrodiol. In the metabolism of 3-F-5-HOMeC, oxidation in the 1-4 ring was inhibited relative to that observed in the metabolism of 5-HOMeC. These results suggest that 5-HOMeC is activated primarily through formation of its 1,2-dihydrodiol. (27 Refs)

7. FORMATION OF TISSUE-BOUND N'-NITROSONORNICOTINE METABOLISM BY THE TARGET TISSUES OF SPRAGUE-DAWLEY AND FISHER RATS.

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Carcinogenesis; 2(10):959-963 1981

The way in which N'-[14C]nitrosonornicotine (NNN) selectively induces tumors in the nasal cavity and esophagus in Sprague-Dawley and Fisher rats was investigated. No major differences in distribution of radioactivity was seen in the two strains. In vivo and in vitro autoradiographic studies following iv injection of 14C-NNN demonstrated localization of tissue-bound metabolites in the mucosa of the nasal cavity, esophagus, tracheo-bronchial tree, and tongue. High levels of unbound radioactivity were found in Zymbal's gland and submaxillary, preputial, lacrimal, and tarsal glands. In vitro experiments in which tissue slices were incubated with 3 uM 14C-NNN, demonstrated marked formation of tissue-bound NNN metabolites by nasal mucosa, liver, and esophagus. Liver tissue also formed bound NNN metabolites, but to a lesser extent than nasal mucosa, whereas levels of bound metabolites in esophagus cultures were almost undetectable. The results suggest that in situ metabolic activation of NNN plays an important role in the pathogenesis of NNN-induced tumors. (13 Refs)

8. METABOLIC ACTIVATION OF A TRYPTOPHAN PYROLYSIS PRODUCT, 3-AMINO-1-METHYL-5H-PYRIDO(4,3-B)INDOLE (TRP-P-2) BY ISOLATED RAT LIVER NUCLEI.

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Cancer Lett; 14(3):261-266 1981

The abilities of nuclei and microsomes to convert 3-amino-1-methyl-5H-pyrido[3,4 -b]indole (Trp-P-2) to an active mutagen were compared. Nuclei from polychlorinated biphenyl or methylcholanthrene-treated rats activated Trp-P-2 and caused a greater number of revertants in the Salmonella mutation test than nuclei isolated from phenobarbitol-treated or non-treated rats. Similar pretreatment effects were observed with microsomal activation. (17 Refs)

9. THE INFLUENCE OF DISULFIRAM AND OTHER INHIBITORS OF OXIDATIVE METABOLISM ON THE FORMATION OF 2-HYDROXYETHYL-MERCAPTURIC ACID FROM 1,2-DIBROMOETHANE BY THE RAT.

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Biochem Pharmacol; 30(21):2983-2987 1981

The mercapturic acid derivative, N-acetyl-S-2-hydroxyethyl-L-cysteine, is a major metabolite of 1,2-dibromoethane in vivo. This compound can be formed via two pathways, both involving a potentially dangerous reactive intermediate. One way involves the intermediacy of bromoacetaldehyde, formed by microsomal oxidation, followed by loss of hydrogen bromide. The second pathway, direct conjugation of 1,2-dibromoethane with glutathione, gives rise to S-2-bromoethyl glutathione. Using several inhibitors of microsomal mixed function oxidases, it was found that under these conditions about 10% of the mercapturic acid derivative formed via direct conjugation. Disulfiram, an inhibitor of aldehyde dehydrogenases, but also of microsomal oxidation, also markedly inhibits the excretion of the mercapturic acid, after administration of a single high dose (1 g/kg) or upon chronic treatment with a low dose (50 mg/kg). The inhibitory effect is max after 10 days of chronic treatment. Administration of large amounts of 1,2-dibromoethane (greater than 0.20 nmole/rat) following a single lower dose of disulfiram (125 mg/kg) also leads to a lower excretion of mercapturic acid metabolite, a phenomenon associated with a decrease in cytochrome P-450 levels. From these results it is concluded that the enhanced carcinogenic effect of the combination disulfiram (chronic)/1,2-dibromoethane is not caused by bromoacetaldehyde, since its formation is completely inhibited under these conditions, but by S-2-bromoethyl-glutathione, although a role for 1,2-dibromoethane itself cannot be excluded. (Author abstract) (27 Refs)

OTHER METABOLISM OF CARCINOGENS

10. NEW PATHWAYS FOR CHLORINATED DIOXINS.

Hay A
Dept. Chemical Pathology, Univ. Leeds, Leeds, England
Nature; 294(5841):514-515 1981

Although 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) is itself active, approx 1% of TCDD is metabolized. TCDD metabolism has been observed in vitro in Golden Syrian hamster hepatocytes. A reaction scheme for the metabolism of TCDD in rats and dogs is presented. Dynamic equilibrium between adipose and other tissues to maintain blood TCDD levels has been postulated for some animals. In humans, the TCDD blood levels are low but long-lasting. The metabolism of other polychlorinated compounds is discussed with reference to the Yusho I and II cases. Carcinogenic risk associated with TCDD is discussed. (no Refs)

11. COMPARATIVE METABOLISM OF 2,6-DIMETHYLNITROSOMORPHOLINE IN RATS, HAMSTERS, AND GUINEA PIGS.

Underwood B, Lijinsky W
Chemical Carcinogenesis Program, Frederick Cancer Res. Center, Frederick, MD, 21701
Cancer Res; 42(1):54-58 1982

The metabolism of N-[3,5-3H]nitroso-2,6-dimethylmorpholine (NDMM) was studied in female Sprague-Dawley rats, Syrian golden hamsters, and guinea pigs. NDMM induces tumors in the esophagus in rats, pancreatic cancer in hamsters, and hemangioendothelial tumors of the liver in guinea pigs. An intragastric dose of NDMM (2 mg, 2 uCi/animal) was rapidly distributed throughout the tissues of both the rat and hamster, with no apparent accumulation of radioactivity in any one tissue. At low dose levels, NDMM was metabolized rapidly by both species. The hamster appeared to metabolize the compound faster than did the rat or guinea pig. An appreciable amount of radioactivity was excreted in the urine in all three species after 8 hr: approx 54% in the hamster; 39% in the rat; and 30% in the guinea pig. During the first 24 hr, only a small percentage of the radioactivity excreted by the hamster, rat, and guinea pig was NDMM (0.8, 2, and 0.5% respectively). High-pressure liquid chromatography analysis of urine collected 24 hr after administration revealed 12 metabolites. Although the urinary metabolites appeared to be similar in all three species, one large difference was the presence of a major urinary metabolite in hamster urine, which was absent or present in only small quantities in the rat and guinea pig. The guinea pig urine also had relatively more radioactivity present in one major fraction than did the hamster or rat. (Author abstract) (22 Refs)

12. COMPARISON OF THE IN VITRO METABOLISM OF N-NITROSOHEXAMETHYLENEIMINE BY RAT LIVER AND LUNG MICROSOMAL FRACTIONS.

Hecker LI, McClusky GA
Chemical Carcinogenesis Program, Frederick Cancer Res. Center, Frederick, MD, 21701
Cancer Res; 42(1):59-64 1982

The in vitro metabolism of N-nitrosohexamethyleneimine by lung and liver microsomes and cytosol from uninduced male Fischer rats is described. Metabolites produced by both organs appeared to be identical. the liver subcellular fractions had a lower Km (0.6 mM) than did lung fractions (3 mM) and metabolized 2.5 to 5x as much nitrosamine per mg protein. Our results, together with those from our earlier studies, indicate that, as the size of the carbon ring increases from nitrosopyrrolidine to nitrosohexamethyleneimine lung microsomes had an increased affinity for the cyclic nitrosamines; there was only a small ef fect with liver enzymes. This suggests that microsomal enzymes that metabolize cyclic nitrosamines in rat livers and lungs are not the same. the first stable alpha-hydroxylation product, 6-hydroxyhexanal, was not detected in reactions involving microsomes alone. Apparently, this compound is rapidly converted to 1,6-hexanediol by liver or lung microsomes. The presence of cytosol was needed for the full conversion of these metabolites to epsilon-hydroxycaproate and max alpha-hydroxylation activity. Epsilon-Aminocaproate was always found in direct proportion to the hydroxyacid, suggesting that both acids arise from the same alpha-hydroxylation event by different breakdown mechanisms. Beta- and gamma-hydroxynitrosohexamethyleneimine were not metabolized significantly by rat liver enzymes and thus, in this species, may be 'detoxification products' of N-nitrosohexamethyleneimine. (Author abstract) (20 Refs)

MODIFICATION OF CARCINOGEN METABOLISM

13. EFFECTS OF BUTYLATED HYDROXYANISOLE ON THE ARYL HYDROCARBON HYDROXYLASE OF RATS AND MICE.

Yang CS, Sydor W, Martin MB, Lewis KF
Dept. Biochemistry, CMDNJ-New Jersey Medical Sch., Newark, NJ, 07103
Chem Biol Interact; 37(3):337-350 1981

The effects of butylated hydroxyanisole (BHA) and butylated hydroxytoluene (BHT) on the aryl hydrocarbon hydroxylase (AHH) activities in the liver, lung and skin of rats and mice have been studied to examine the possible mechanisms of the anticarcinogenic actions of these compounds. Both compounds inhibit the hydroxylase activities of hepatic microsomes and nuclei, with BHA a more potent inhibitor than BHT. The AHH of lung microsomes is inhibited to a lesser extent by BHA and BHT than that of the liver. The AHH activities of both liver and lung microsomes become less susceptible to the inhibition after pretreatment of the animals with 3-methylchoanthrene (MC) or 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) but phenobarbital (PB) pretreatment does not produce such an effect. In skin homogenates, however, the AHH activities of control rats and mice are not inhibited by BHA and BHT. The only skin sample which is inhibited by BHA and BHT is that from TCDD-pretreated mice. It has been established that the extent of inhibition with different samples is related to the concentration of BHA in the incubation but not to the amounts or specific activities of microsomes used. Double reciprocal plots suggest that BHA exerts a mixed inhibition on the hydroxylase of liver microsomes with Ki of 7.7 uM. Analysis of the metabolites of benzo[a]pyrene (BP) shows that BHA inhibits the formation of various metabolites uniformly without changing the regioselectivity of the enzyme system. The mechanism of inhibition has also been studied with a reconstituted AHH system consisting of cytochrome P-450 (P-450), reductase and phospholipid. The system with P-450 isolated from PB-induced microsomes is inhibited to a much greater extent than that with MC-induced P-450. The results indicate that the inhibitory action of BHA is dependent on the species of the animal, tissue types and treatment with inducers. (Author abstract) (42 Refs)

14. COMPARISON OF THE EFFECT OF BUTYLATED HYDROXYTOLUENE ON N-NITROSOMETHYLUREA AND 7,12-DIMETHYLBENZ(A)ANTHRACENE-INDUCED MAMMARY TUMORS.

King MM, McCay PB, Kosanke SD
Biomembrane Res. Lab., Oklahoma Medical Res. Foundation, 825 N.E. 13th St., Oklahoma City, OK, 73104
Cancer Lett; 14(3):219-226 1981

The effects of butylated hydroxytoluene (BHT) on nitrosomethylurea (NMU)- and 7,12-dimethylbenz(a)anthracene (DMBA)-induced rat mammary tumors were examined. Female Sprague-Dawley rats were fed either control diets or diets plus 0.3% BHT, and further divided into NMU-treated, DMBA-treated, or nontreated groups. DMBA was administered at 10 mg in 1 ml stripped corn oil intragastrically at 50 days of age. NMU was administered at 5 mg/100 g body wt iv in the tail vein at 50 days of age. A 100% incidence of tumors was seen in rats treated with DMBA and on the control diet. The incidence was reduced to 54% by addition of BHT to the diet. No difference in tumor incidence was seen in NMU-treated animals with or without addition of BHT. The differences in tumor prophylaxis may reflect the fact that DMBA is metabolized by the monooxygenase system but NMU is not. (30 Refs)

15. ROLE OF NUTRITIONAL FACTORS IN REALIZATION OF BIOLOGICAL EFFECTS OF XENOBIOTICS.

Sharmanov TS
Kazakh Branch, Inst. Nutrition, Alma-Ata, USSR
Vopr Pitan; (5):51-57 1981

The role of nutritional factors in the metabolism of pesticides, nitrosamines, and aflatoxins is reviewed. Nitrites present in canned meat or fish can react with exogenous amines to yield carcinogenic nitroso compounds. Dietary deficiency of vitamin C and essential amino acids enhanced the carcinogenic activity of N-nitrosopyperidine in guinea pigs. Deficiency of the essential amino acids and retinol enhanced the incidence of aflatoxin B1-induced tumors in rats. (33 Refs) (In RUS)

MUTAGENICITY OF ACTIVATED METABOLITES OF CARCINOGENS

16. STRUCTURE-MUTAGENICITY ANALYSIS WITH THE CHO/HGPRT SYSTEM.

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Food Cosmet Toxicol; 19(5):617-621 1981

A mutational system which affects hypoxanthine-guanine phosphoribosyl transferase (HGPRT) activity in Chinese hamster ovary (CHO) cells, the CHO/HGPRT system, was used to study the structure-mutagenicity of 10 carcinogenic alkylating agents and 6 platinum(11) compounds. Cytotoxic and mutagenic effects of the alkylating agents decreased with increasing size of the alkylating group. When the relationship between DNA alkylation and mutation at the hgprt locus of N-nitroso-N-methylurea (MNU) and N -nitroso-N-ethylurea (ENU) was studied, MNU, on an equimolar basis, had 15x the alkylating activity of ENU but only 3x the mutagenic activity. Ethylation of DNA by ENU resulted in greater than 4x the number of mutagenic lesions than did methylation by MNU. cis-Dichlorodiammine platinum(11) was the most mutagenic among the six platinum(1)chloroammines, while its steric isomer, the trans form, was non-mutagenic. Mutagenicity and cytotoxicity differ in their reactivity of DNA binding. The mutation induction by the cis isomer as a function of treatment concentration was 2400x that of the trans isomer. However, the cis isomer bound only 3x more to cellular DNA than did the trans isomer. The mutant yield per molecule bound to DNA was 800x larger for the cis than for the trans isomer. Cytotoxicity per DNA lesion was a factor of 9 greater for the cis than for the trans isomer. These studies demonstrate that both the quantity and quality of DNA adducts affect mutagenicity and cytotoxicity. The CHO/HGPRT system is useful for studying genetic aspects of toxicology and for relating molecular parameters necessary for mutagenic and cytotoxic activities. (26 Refs)

17. ETHANOL- OR ACETONE-PRETREATMENT OF MICE STRONGLY ENHANCES THE BACTERIAL MUTAGENICITY OF DIMETHYLNITROSAMINE IN ASSAYS MEDIATED BY LIVER SUBCELLULAR FRACTION, BUT NOT IN HOST-MEDIATED ASSAYS.

Glatt H, De Balle L, Oesch F
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Carcinogenesis; 2(10):1057-1061 1981

The effect of acetone or ethanol pretreatment of mice on dimethylnitrosamine (DMN) mutagenicity in host- and liver subcellular fraction-mediated assays was investigated. Salmonella typhimurium TA 92 was used in both the in vitro S9-mediated assay and in the in vivo host-mediated assay because it was more sensitive than TA 1535, TA 100, or Escherichia coli WP2 uvrA and because it possesses an intact polysaccharide layer. Pretreatment of C57BL/6J mice with either 45 millimoles of acetone or 30-60 millimoles of ethanol per kg potentiated DMN mutagenicity in S9 mix-mediated assays. At low DMN concentrations (100 uM), greater than 100x more mutants were induced with S9 mix from acetone-treated mice than with S9 mix from controls. Ethanol had a similar, but weaker, effect. In the host-mediated assay, DMN was a potent mutagen, but this effect was not enhanced by pretreatment with either acetone or ethanol. In general, mutagenicity was slightly lower in acetone-pretreated animals than in controls. A possible explanation for the differences observed in vitro and in vivo may be that in vitro the activity of the dilute metabolizing system is limiting for the activation of DMN, whereas in vivo DMN is completely metabolized in both induced and noninduced animals. (16 Refs)

18. MUTAGENICITY PATTERNS RESULTING FROM THE REACTION OF NITRITE WITH ICR-170.

de Flora S, Zanacchi P, Camoirano A, Bennicelli C
Inst. Hygiene, Univ. Genoa, Via Pastore 1, 16132 Genoa, Italy
Mutat Res; 103(1):13-17 1982

ICR-170, 2-methoxy-6-chloro-9-(3-[ethyl-2-chloroethyl] aminopropylamino) acridine.2HCl reacted with nitrite in an acidic environment to form a mutagenic derivative. Suitable soln of sodium nitrite were preincubated, either separately or mixed together, with 5 ml of human gastric juice or 0.15 M NaCl adjusted to various pH values. After 60 min at 37 C, 1 ml of 0.2 M phosphate-buffered saline, pH 7.4, was added. The resulting mixtures (0.5 ml/plate) were assayed in the plate incorporation test using various Salmonella his- strains. All the strains except TA1535 were reverted by ICR-170. TA1537 was most sensitive, a finding typical for acridine derivatives. Mutagenicity of TA1537 and of the other positive strains (TA 1538, TA98, and TA100) was increased by rat liver S9 fractions. The metabolic effect was less pronounced than previously reported for the same compound lacking an ethyl group (ICR-191). Direct frameshift activity of ICR-170 decreased in all positive strains after its reaction with nitrite. Such an activity was replaced by an S9-requiring mutagenic response in TA1538, TA98, and TA100; the response correlated with the amounts of both ICR-170 and nitrite. The study suggests that nitrosation of ICR compounds occurs at the only site where ICR-170 and ICR-191 are different, ie, at the terminal nitrogen of the nitrogen-mustard moiety. (10 Refs)

19. ENHANCEMENT OF BENZO(A)PYRENE INDUCED SISTER CHROMATID EXCHANGES AS A CONSEQUENCE OF GLUTATHIONE DEPLETION IN VIVO.

Bayer U, Younes M, Siegers CP
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Toxicol Lett; 9(4):339-343 1981

The effect of decreased hepatic glutathione (GSH) concentration on sister chromatid exchange (SCE) in vivo in the bone marrow of Chinese hamsters induced by 3,4-benzo(a)pyrene (BaP) was examined. SCE were studied in differentially stained bone marrow after sc implantation of 50 mg bromodeoxyuridine, ip injection of phorone (125 or 250 mg/kg body wt) or olive oil, and injection of BaP (50 or 100 mg/kg body wt). Induction of SCE by BaP after pretreatment with 125 mg/kg phorone increased to an av 5.9 (50 mg/kg BaP) and 7.0 (100 mg/kg BaP) SCE/cell. Pretreatment with 250 mg/kg phorone resulted in SCE values of 6.8 (50 mg/kg BaP) and 7.6 (100 mg/kg BaP). Hepatic GSH content and GSH S-transferase activities were also studied after injection of phorone (125 or 250 mg/kg body wt) or olive oil. Pretreatment with 125 mg/kg phorone led to a decrease in the GSH content to 1.2 micromole/g liver but had no significant effect on GSH S-transferase activities. Pretreatment with 250 mg/kg phorone gave no further effect. Apparently the amount of GSH available is one factor responsible for the degree of detoxication of BaP. The higher SCE frequency in the absence of GSH is probably a consequence of an increased amount of reactive, mutagenic BaP metabolites. (18 Refs)

20. INDUCTION OF GENE MUTATIONS BY BENZ(A)PYRENE DURING METABOLIC ACTIVATION.

Pashin IuV, Bakhitova LM
Inst. General Genetics, Moscow, USSR
Biull Eksp Biol Med; 91(9):327-329 1981

The mutagenic activity of benz(a)pyrene (BP) was studied in Chinese hamster diploid cell line V-79. Incubation of the cell culture in media containing BP (5-25 ug/ml) and microsomal activating mixture resulted in a dose-dependent increase in the yield of gene mutations. (13 Refs) (In RUS)

21. CYTOTOXICITY AND MUTAGENICITY OF DINITROTOLUENES IN CHINESE HAMSTER OVARY CELLS.

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Mutat Res; 103(1):53-59 1982

Technical grade dinitrotoluene (DNT), a mixture composed predominantly of 2,4-and 2,6-DNT but containing lesser amounts of 2,3-, 2,5-, 3,4-, and 3,5-DNT, was tested for mutagenicity using the Chinese Hamster Ovary/Hypoxanthine-Guanine Phosphoribosyl Transferase system. Induction of mutation to 6-thioguanine (TG) resistance was tested in the presence and absence of microsomal preparations (PMS) from rats pretreated with the mixed function oxidase inducer Aroclor 1254. Marked differences in isomeric cytotoxicity were observed. However, neither technical grade DNT nor any of the purified isomers resulted in a significant increase in the TG-resistant fraction of surviving cells with or without PMS. (19 Refs)

22. MUTAGENICITY OF GLYCEROL CHLOROHYDRINES AND OF THEIR ESTERS WITH HIGHER FATTY ACIDS PRESENT IN PROTEIN HYDROLYSATES.

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Dept. Biochemistry and Microbiology, Inst. Chemical Technology, 166 28 Prague 6, Czechoslovakia

Mutat Res; 103(1):77-81 1982

Mutagenicity of the glycerol chlorohydrines 3-chloro-1,2-propanediol (3CP) and 1,3-dichloro-2-propanol (1,3DP), and of their esters with palmitic and oleic acids, was tested with strains of Salmonella typhimurium and Escherichia coli. 3CP and 1,3DP caused base substitutions in S typhimurium TA1535 with and without metabolic activation. Metabolic activation in vitro with S9 mix did not influence the mutagenic effect of non-toxic concentrations of the glycerol chlorohydrines, but it led to a strong increase in the amount of mutants with those chlorohydrine concentrations causing strong suppression of background growth without metabolic activation. Difference in the growth of wild-type and repair-deficient strains of E coli was observed only for 1,3DP with S9 mix. Esters of both 3CP and 1,3DP with fatty acids had smaller mutagenic effects than unesterified compounds. (16 Refs)

23. SYNTHESIS AND MUTAGENIC ACTIVITY OF ALKYL DERIVATIVES OF 2-AMINO-9H-PYRIDO[2,3-B]INDOLE.

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Agric Biol Chem; 45(9):2031-2035 1981

Synthesis and mutagenic activity of 2-amino-3-methyl-9H-pyrido[2,3-b]indole (MeAC) and other alkyl derivatives of 2-amino-9H-pyrido[2,3-b]indole (AC) were investigated; identification of 2-amino-3-ethyl-9H-pyrido[2,3-b]indole (EtAC) in the pyrolysate of soybean globulin is reported. Ames tests and rec-assays gave similar results with MeAC and AC, showing substantially the same mutagenic activity as MeAC and EtAC obtained from soybean globulin. An increase in number of carbons in the alkyl group was accompanied by a decrease in mutagenic activity. Activation of the C-2 amino group by liver-homogenate may have been hindered sterically by a neighboring substituent, as possibly was the binding of DNA and the activated compound. (11 Refs)

24. MUTAGENIC ACTIVITY OF ISONIAZID AND ITS METABOLITES IN DIFFERENT TEST SYSTEMS.

Menon MM, Maru GB, Bhide SV
Carcinogenesis Div., Cancer Res. Inst., Bombay 400 012, India
Indian J Exp Biol; 19(10):939-942 1981

The mutagenic activity of isoniazid (INH) and its metabolites was examined using the Ames test system employing Salmonella typhimurium strains as well as two in vivo mammalian test systems (dominant lethal test and testicular DNA biosynthesis inhibition test). Possible prevention of mutagenic effects of INH using INH antitoxicants was also studied. INH without rat liver S9 mixture was mutagenic towards TA 100 and TA 1535. INH was not mutagenic to TA 92 or TA 98. Use of para-amino salicylic acid with INH significantly increased the number of revertants obtained. Two INH hydrazine metabolites, hydrazine sulfate (HS) and monoacetyl hydrazine (MAH), were mutagenic, HS for strains TA 92, TA 100, and TA 1535, and MAH for TA 100 and TA 1535. Negative results were obtained with diacetyl hydrazine and acetyl isoniazid. Of the three chemicals found to be positive, HS showed max mutagenicity in the presence of S9. Folic acid and pyridoxine slightly inhibited INH mutagenicity. The response of INH and HS was negative in the dominant lethal test. DNA synthesis in mouse testis was inhibited by INH, HS, MAH, and acetyl INH. It was concluded that the Ames test and the testicular DNA synthesis inhibition test show a good correlation in displaying mutagenicity of INH, HS, and MAH. (21 Refs)

25. THE ACTION OF TRANSITION METALS ON THE GENOTOXICITY OF SIMPLE PHENOLS, PHENOLIC ACIDS AND CINNAMIC ACIDS.

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Environmental Carcinogenesis Unit, British Columbia Cancer Res. Centre, 601 W. 1 0th Ave., Vancouver V5Z 1L3, Canada
Cancer Lett; 14(3):251-260 1981

The capacity of several phenolic compounds to induce chromatid breaks and exchanges in Chinese hamster ovary cells, and the modulating effect of the transition metals Cu++ and Mn++ on the clastogenicity of phenolics were examined. All dihydroxylated and trihydroxylated phenolics induced chromatid breaks and exchanges. Addition of S9 mixture or transition metals enhanced clastogenicity of some phenolics but reduced it in others. (35 Refs)

26. CONVERSION OF CHLORINATED NITROBIPHENYL ETHERS AND THEIR DERIVATIVES TO MUTAGENS BY WHITE-SPOTTED CHAR, SALVELINUS LEUCOMAENIS, LIVER HOMOGENATE.

Miyauchi M, Takagi M
Lab. Food Hygiene, Faculty of Fisheries, Hokkaido Univ., Hakodate 041, Japan
Bull Jpn Soc Sci Fish; 47(2):243-250 1981

Mutations were induced by p-nitrobiphenyl ether, its chlorinated forms, and their nitroso derivatives in a Salmonella typhimurium assay without liver homogenate. Liver homogenate from the white-spotted char increased mutagenicity of the compounds slightly and greatly increased the mutagenicity of amino derivatives. (23 Refs)

27. EFFECT OF CALCIUM PHOSPHATE AND ALUMINA C GAMMA GELS ON THE MUTAGENICITY AND CYTOTOXICITY OF DIMETHYLNITROSAMINE AS STUDIED IN THE CHO/HGPRT SYSTEM.

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Mutat Res; 84(1):147-156 1981

The effects of calcium phosphate and alumina C gamma gels in the S9 activation system on the cytoxicity and mutagenicity of dimethylnitrosamine (DMN) were studied in the Chinese hamster ovary cell hypoxanthine-guanine phosphoribosyl transferase system. The calcium phosphate gel in the Ca/Mg-S9 mix was essential in potentiating the mutagenic activity of DMN. Varying amounts of CaCl2 were added to the Mg-S9 salts before adding S9 protein to determine whether the cytotoxic and mutagenic effects of DMN were due to Ca++ in the Ca/Mg-S9 mix. Increasing amounts of CaCl2 in the Mg-S9 mix made up in phosphate buffer caused increased cell killing and mutant induction; the max was observed at a Ca++ concentration of 10 milliM. Increasing concentrations of commercial preparations of calcium phosphate and tricalcium phosphate gels also increased cytotoxicity and mutagenicity of DMN. Alumina C gamma gel in Mg-S9 mix was just as effective as calcium phosphate gel in activating DMN. The cytotoxicity and mutation frequency of DMN were almost identical to those obtained with calcium phosphate gel. Diethylaminoethyl cellulose caused some increase in DMN-induced cytotoxicity but not -mutagenicity. Increasing the contact time between the S9 protein and the S9 salts increased the efficacy with which the S9 mix activated DMN; this was indicative of an adsorptive process by calcium phosphate gel. The results indicated that calcium phosphate or alumina C gamma gels can mimic the effects of cytosolic factors on the microsomes or by concentration of demethylase activity around the cells. (21 Refs)

28. INVESTIGATIONS ON THE MUTAGENICITY OF PRIMARY AND SECONDARY ALPHA-ACETOXYNITROSAMINES WITH SALMONELLA TYPHIMURIUM: ACTIVATION AND DEACTIVATION OF STRUCTURALLY RELATED COMPOUNDS BY S-9.

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Carcinogenesis; 2(10):991-997 1981

Mutagenicity of 12 primary and secondary alpha-acetoxynitrosamines (AANs) was investigated to elucidate the influence of structure on the extent of their biologic activity. Aldehydes presumably arising after AAN cleavage were nonmutagenic in Salmonella typhimurium strain TA 1535. After hydrolysis, AANs were mutagenic, indicating that AAN mutagenicity is caused mainly by the alkylating species generated after cleavage of the acetates and not by the corresponding aldehydes. More stable primary AANs were less mutagenic at equimolar concentrations than the respective secondary compounds. Addition of S-9 mix caused both activation and deactivation in an unexpected structure-related pattern: An exactly opposite influence of S-9 components on mutagenicity was observed for each pair of primary and secondary AANs containing the same alkylating species. Pairs of compounds with both methylating and ethylating properties were influenced differently by addition of S-9 than those with propylating or butylating properties. This demonstrates how different chemical properties of intermediate forms may influence biologic activity of otherwise similar compounds. (28 Refs)

29. CYTOTOXIC AND MUTAGENIC EFFECTS OF STERIGMATOCYSTIN ON CULTURED CHINESE HAMSTER CELLS.

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Carcinogenesis; 2(10):945-949 1981

Cytotoxicity and mutagenicity of sterigmatocystin (STC) on cultured Chinese hamster cells were investigated in the presence and absence of a metabolic activation system. STC, when applied directly to V79 cells, was cytotoxic and induced 8-azaguanine-resistant mutations in a dose- and time-dependent manner. Effects of STC were enhanced markedly by 1%, 5%, or 20% S15 (polychlorinated biphenyl-induced rat liver microsomes) and other cofactors. In the presence of 1% S15, STC concentration required to induce cytotoxicity was approx 20x less than that required when S15 was applied directly; 1% STC was more cytotoxic and more mutagenic than either 5% or 20% STC. Analysis on the basis of equitoxic levels demonstrated that there was little difference in the degree of mutagenicity induced by direct treatment with STC and treatment with STC in the presence of S15. The effects of STC were enhanced in proportion to the duration of the treatment period. Treatment for shorter periods, however, was more effective than that for longer periods. The decreased effectivness was not attributable to instability of STC. (21 Refs)

30. MUTAGENICITY OF OIL-SHALE ASH.

Whong WZ, Sorenson WG, Elliott JA, Stewart J, Simpson J, Piacitelli L, McCawley M, Ong T

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Mutat Res; 103(1):5-12 1982

Three oil shale samples were analyzed for mutagenicity in four test systems after extraction with solvents. In Salmonella typhimurium, extracts were highly mutagenic with Ames his reversion and ara-resistant systems; mutation induction was independent of metabolic activation and was of the frameshift type. The extracts showed substantial killing effect, but they failed to induce ad-3 reversion in Neurospora crassa, gene conversion and mitotic crossing-over in Saccharomyces cerevisiae, or TGr mutation in cultured CHO cells. (14 Refs)

31. FAILURE OF CHLOROFORM TO INDUCE CHROMOSOME DAMAGE OR SISTER-CHROMATID EXCHANGES IN CULTURED HUMAN LYMPHOCYTES AND FAILURE TO INDUCE REVERSION IN ESCHERICHIA COLI.

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Food Cosmet Toxicol; 19(5):651-656 1981

Mutagenicity of chloroform in Escherichia coli strains WP2p and WP2uvrA-p was tested using both plate incorporation and liquid pre-incubation. In addition, ability of chloroform to induce sister-chromatid exchanges (SCE) in human lymphocytes in the presence of S-9 rat-liver microsomes was tested. Chloroform did not induce reversions in WP2p or WP2urvA-p in either of the assays used. In contrast, both positive control chemicals used (N-methyl-N'-nitro-N-nitrosoguanidine and 2-aminoanthracene) were mutagenic. Benzo-(a)pyrene at concentrations up to 10 ug/ml induced significant increases in SCE in human lymphocytes in the presence or the absence of S-9, whereas chloroform (25-400 ug/ml) plus S-9 induced a significant increase in SCE in cells from the same donor only at the 50-ug/ml dose. Whereas the positive control gave reasonable dose-response trends [correlation coefficient (r) 0.995 and 0.782 with and without S-9, respectively], this was not the case for chloroform (r = 0.206). Failure of chloroform to induce any type of mutagenic event in vitro raises questions in relation to prediction of cancer risk. (19 Refs)

32. FLAVONOIDS, MUTAGENS, AND CITRUS.

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ACS Symp Ser; 170:43-59 1981

Data on the mutagenicity of flavonoids are reviewed. Of all classes of flavonoid s, mutagenicity has been demonstrated only for some of the flavonols. Quercetin had the highest mutagenic activity in the Ames test in Salmonella typhimurium. The validity of the Ames test, however, depends on the activating agents used. Flavonols occur in almost all higher plant tissues and are common in human diets. The most common flavonols are quercetin and kaempferol, which almost always occur in the form of glycosides, which are nonmutagenic. Metabolism of quercetin glycosides is probably carried out along several pathways by intestinal microflora. Any occurrence of mutagenic quercetin aglycone is probably fleeting at most. Animal feeding studies of quercetin carcinogenicity have produced contradictory results. No evidence of absorption of free quercetin by the human gut has been found. Citrus fruits contain a wide variety of flavonoids. Any mutagenic activity of flavonols is probably affected by the presence of other flavonoids. Flavonol apparently present minimal risk in human diets. (46 Refs)

BINDING OF CARCINOGENS AND THEIR METABOLITES TO MACROMOLECULES

33. EFFECTS OF 5-METHYLNICOTINAMIDE ON MOUSE L1210 CELLS EXPOSED TO N-METHYL-N-NITROSOUREA: MUTATION INDUCTION, FORMATION AND REMOVAL OF METHYLATION PRODUCTS IN DNA, AND UNSCHEDULED DNA SYNTHESIS.

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Carcinogenesis; 2(10):1013-1017 1981

Alkylation of L1210 DNA by N-methyl-N-nitrosourea (MNU) was measured, and the effects of 5'-methylnicotinamide (5MeN) on removal of methylated purines, on unscheduled DNA synthesis, and on induction of 6-thioguanine (6TG)-resistant mutants were examined. The loss of colony-forming ability of L1210 cells caused by MNU was potentiated 2.8-fold in the presence of 1 milliM 5MeN. 5MeN reduced the frequency of 6TG-resistant mutants induced by MNU: In two experiments, the induced mutation frequencies of cells not treated with 5MeN were 15.6 and 12.1 mutants per 10(4) surviving cells per milliM MNU compared with 7 mutants per 10(4) survivors per milliM MNU for mutations expressed and selected in the presence of 5MeN. 7-Methylguanine removal from DNA by MNU was unaffected by 5MeN, whereas O6-methylguanine (O6-MeG) was removed from 5MeN-treated cells at a significantly higher rate (half-life 28 hr) than from untreated cells (half-life 46 hr). 5MeN had no effect on inhibition of normal replicative DNA synthesis by 0.2 milliM hydroxyurea, whereas it stimulated unscheduled DNA synthesis under similar conditions. The observation that 5MeN reduces the frequency of 6TG-resistant mutants induced by MNU and enhances the rate of O6-MeG removal is consistent with this being a promutagenic lesion in L1210 cells. (48 Refs)

34. TISSUE-DEPENDENT ENZYME-MEDIATED REPAIR OR REMOVAL OF O-ETHYL PYRIMIDINES AND ETHYL PURINES IN CARCINOGEN-TREATED RATS.

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Carcinogenesis; 2(10):1069-1073 1981

Ten-day-old BD IX rats were injected with radiolabeled N-ethyl-N-nitrosourea (EtNU: 69.4 ug/kg, ip), and the sites and proportions of ethyl products, as well as their removal and repair, in DNA from various tissues was examined. One hr after carcinogen injection, DNA of brain, liver, and other pooled organs (spleen, lung, thymus, muscle, and intestine) showed similar proportions of the derivatives quantitated (O6-ethyl [Et] guanine [G], 7EtG, 3-Et adenine [A], O2-Et thymine [T], O4-EtT, O2-Et cytosine [C], and ethylphosphotriesters). During the 75 hr after carcinogen administration, most ethylated bases were poorly removed (or, in the case of O4-EtT, not at all) from DNA in the brain (the target tissue of EtNU carcinogenicity), and from DNA in the tissue pool. Removal from the brain appeared to cease after 25-50 hr. Kinetics of O6-EtG removal in brain and in the tissue pool were similar, except that there was a rapidly exhausted early and partial repair capability in brain. O-alkyl products were removed from the liver at progressively increasing rates over the entire 75-hr period. The accelerated loss of O2-EtT, O4-EtT, and O2-EtC may have been due either to an increase in hepatic protein synthesis as a result of recovery from EtNU-induced inhibition or to induction of an O-alkyl pyrimidine-specific enzyme. Triester levels remained almost unchanged in all tissues examined. However, the small decrease in the triester level observed in liver DNA suggested a half-life of greater than 1 wk. Any or all persistent promutagenic derivatives (O6-EtG, O2-EtT, O4-EtT, O2-EtC) may be important in initiation of carcinogenesis by somatic mutation. (45 Refs)

35. HOT SPOTS OF FRAMESHIFT MUTATIONS INDUCED BY THE ULTIMATE CARCINOGEN N-ACETOXY-N-2-ACETYLAMINOFLUORENE.

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Nature; 294(5842):657-659 1981

An important step in carcinogenesis is thought to be the initial attack of the DNA molecule by a so-called ultimate carcinogen. More than 90% of the carcinogens tested have been found to be mutagens in bacterial systems. The covalent binding of the ultimate carcinogen to the DNA bases or phosphate groups creates a premutational lesion that in vivo is processed by the repair, replication and recombination enzymes, and eventually may be converted into a mutation. Being interested in the way that an initial premutational event is converted into a stable heritable mutation, we have sequenced stable mutations in a gene that has formed covalent adducts in vitro with N-acetoxy-N-2-acetylaminofluorene (N-AcO-AAF, a model for the ultimate metabolite of the rat liver carcinogen 2-acetylaminofluorene AAF). We show here that the mutations are mainly frameshifts involving G-C base pairs, and that certain base pairs (hotspots) are affected at relatively high frequencies. These results fit a model in which N-AcO-AAF-modified guanine acts as a non-coding base that during replication results in deletion of the modified residue. (Author abstract) (23 Refs)

36. IN VITRO REACTION OF THE CARCINOGENIC DERIVATIVE N-ACETOXY-7-ETHYL-N-2-ACETYLAMINOFLUORENE WITH DNA. A SPECTROSCOPIC STUDY.

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Carcinogenesis; 2(10):1019-1025 1981

Reaction in vitro of DNA with N-acetoxy-7-ethyl-N-acetylaminofluorene (N-AcO-EtAAF) was compared with N-acetoxy-N-acetyl-2-aminofluorene (NAcO-AAF). Introduction of an ethyl group at position 7 of the fluorene ring induces an increase of reaction of this (model) metabolite of the carcinogen 2-acetoxy-2-aminofluorene (2-AAF) toward DNA and its constituents. UV absorption and circular dichroism spectroscopic methods were used to characterize the DNA reacted with N-AcO-EtAAF (DNA-EtAAF). Results indicate some conformational similarities between native DNA-EtAAF and DNA-AAF such as the presence of destabilized regions around the bound carcinogen and of stacking interactions between these residues and the adjacent nucleotides. Important differences appear to exist between adducts or modified sequences in native as compared to denatured DNA (contrary to DNA-AAF and DNA bearing covalently bound 2-aminofluorene). (19 Refs)

37. MODULATION OF THE COVALENT BINDING OF ARYL HYDROCARBON METABOLITES TO DNA IN VITRO AFTER TREATMENT OF RATS AND MICE WITH TRANS-STILBENE OXIDE.

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Carcinogenesis; 2(10):1049-1056 1981

Effects of trans-stilbene oxide (TSO) on in vitro microsome-mediated binding of benzo(a)pyrene (BP) and 7,12-dimethylbenz(a)anthracene (DMBA) to purified DNA were investigated. Chromatograms of enzyme digests of DNA obtained from incubation of labeled BP metabolites with hepatic microsomes from TSO-treated Sprague-Dawley rats showed a decrease in peak H (nucleoside-bound 9-hydroxy-BP-4,5-oxide) without any significant modification of peaks E (nucleoside-bound syn- and anti-BP-7,8-diol-9,10-epoxide) or G (nucleoside-bound BP-4,5-oxide). In vitro addition of the epoxide hydrolase inhibitor 1,1,1-trichloropropene 2,3-oxide (TCPO) produced 2.8-and 3.2-fold increases, respectively, in peaks G and H in microsomes from TSO-treated rats compared with those from controls. BP-metabolite-deoxyribonucle oside profiles obtained with microsomes from rats treated with BP (40 mg/kg) alone showed considerable covalent binding of BP-7,8-diol-9,10-epoxide and 9-hydroxy-BP-4,5-oxide; treatment with both BP and TSO (3 x 400 mg/kg) decreased binding to 45% and 25%, respectively. Microsomes from TSO-treated Swiss mice showed levels of BP-4,5-oxide and 9-hydroxy-BP-4,5-oxide binding that were 1.6-and 1.4-fold, respectively, greater than levels in microsomes from controls. The heights of peaks E, G, and H for C57BL/6 mice treated with TSO and BP were 53%, 60%, and 69% of the values obtained for mice treated with BP alone. After incubation of DNA with 3H-DMBA and BP- or TSO plus BP-treated rat liver microsomes, dual induction by BP and TSO was found to decrease DMBA metabolite binding to DNA, compared with induction by BP alone. The studies demonstrated the ability of TSO to increase the rate of oxidation at the K-region, due to induction of specific monooxygenases, and its ability to increase the rate of deactivation of epoxide intermediates by inducing microsomal epoxide hydrolase activity. The effects of TSO were similar for both substrates examined. (29 Refs)

38. METABOLISM OF 1-NITROPYRENE AND FORMATION OF DNA ADDUCTS IN SALMONELLA TYPHIMURIUM.

Messier F, Lu C, Andrews P, McCarry BE, Quilliam MA, McCalla DR
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Carcinogenesis; 2(10):1007-1011 1981

1-Nitropyrene was slowly reduced by intact cells of Salmonella typhimurium to 1-aminopyrine and N-acetyl-1-aminopyrene, as well as six minor metabolites. When tritiated nitropyrene was metabolized, some radioactivity was bound to DNA, with a time course similar to that for reduction of 1-nitropyrene. Max binding levels were of the order of one molecule of nitropyrene per 10(6) nucleotides in DNA. Results of DNA-binding experiments with nitroreductase-deficient strain TA100 F50 suggested that reductase activity present in TA100 (wild-type for nitroreductase) but absent from the F50 mutant is involved in the reductive 'activation' of 1-nitropyrene. Upon enzymatic hydrolysis of DNA, radioactivity appeared in low mol wt material, much of which eluted before the normal nucleosides. This material most likely represented an adduct or adducts formed between nitropyrene metabolites and nucleosides in DNA. Results with a uvr+ strain in this study, as well as results of previous studies, suggested that these adducts are subject to removal in strains proficient in excision repair. (18 Refs)

39. ALKYLATION OF N2 IN DEOXYGUANOSINE BY DEHYDRORETRONECINE, A CARCINOGENIC METABOLITE OF THE PYRROLIZIDINE ALKALOID MONOCROTALINE.

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Cancer Res; 42(1):8-14 1982

Dehydroretronecine, an antimitotic and carcinogenic agent, reacted with the deoxyguanosine at pH 7.4 in vitro to yield in nearly equal quantities two major adducts, which were isolated by thin-layer and high-pressure liquid chromatography. The adducts were stable at pH 8.7 and 30 C for at least 24 hr, showed pKas at acidic and alkaline pHs, reacted with 4-(p-nitrobenzyl)-pyridine, had a nonexchangeable guan-8-yl proton, and contained equimolar quantities of the pyrrole and nucleotide moieties. From the above data and comparison of proton magnetic resonance spectra of dehydroretronecine, deoxyguanosine, and the adducts, both products were identified as derivatives with a bond between C-7 of dehydrosupinidine and N2 of deoxyguanosine. Mass spectral fragmentation patterns and infrared and UV absorbance spectra were also consistent with N2 substitution. Circular dichroism spectra established the identities of each of the adducts as 7-(deoxyguanosin-N2-yl)dehydrosupinidine; they are enantiomeric at C-7. These results demonstrate that the reactive electrophile derived from protonated dehydroretronecine readily alkylates the N2 position of deoxyguanosine at C-7 in an SN1 reaction to yield a racemic mixture of products. (Author abstract) (34 Refs)

40. THE DISTRIBUTION OF BENZO(A)PYRENE DNA ADDUCTS IN MAMMALIAN CHROMATIN.

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Nucleic Acids Res; 9(21):5533-5552 1981

This paper describes the distribution of DNA-lesions generated by the potent carcinogen benzo(a)pyrene (BP) or its ultimate metabolic derivative 7alpha,8beta,di-hydroxy-9beta,10beta-epoxy-7,8,9,10 tetrahydrobenzo(a)pyrene (BPDE) within mammalian chromatin using the enzymic probe micrococcal nuclease. We have shown that the progress of the nuclease on naked DNA is unaffected by the presence of the hydrocarbon lesion at moderate extents of digestion. Digestion of nuclei isolated from murine erythroleukemic cells immediately following BPDE treatment, and analysis of micrococcal nuclease resistant DNA by TCA precipitation, hydroxyapatite chromatography and gel electrophoresis demonstrates a non-random distribution of lesions. Approx 3x more binding occurs on the linker DNA regions between nucleosome cores than on the nucleosome core DNA itself. A similar result was obtained with BPDE treated primary mouse embryo cells; however nuclei isolated from these cells after prolonged treatment with BP (to allow metabolic activation) showed no such preferential binding. Post-treatment incubation of PBDE-treated cells shows that this difference can be accounted for by the loss of preferential localization with time. (Author abstract) (33 Refs)

ALTERATION OF MIXED FUNCTION OXIDASES BY CARCINOGENS

41. DEVELOPMENTAL ONSET OF MIXED-FUNCTION OXIDASE ACTIVITY IN PREIMPLANTATION MOUSE EMBRYOS.

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Biology Div., Oak Ridge Natl. Lab., Post Office Box Y, Oak Ridge, TN, 37830
Proc Natl Acad Sci USA; 78(11,part2):6991-6995 1981

Two-cell embryos, obtained from the C57BL/6N and DBA/2N strains, were cultured in media that supported in vitro differentiation and that contained [3H]benzo[a]pyrene. High-pressure liquid chromatography of the activated intermediates formed during in vitro early embryonic development indicated that the onset of polynuclear aromatic hydrocarbon activation coincided with blastocyst formation. Comparison of individual oxygenated intermediates metabolically formed from embryos genetically 'responsive' or 'nonresponsive' to aromatic hydrocarbons revealed significant quantitative differences in the production of dihydrodiol, quinone, and phenolic derivatives. In addition to exhibiting basal mixed-function oxidase activity, blastocysts were also responsive to enzymatic induction when exposed to 2,3,7,8-tetrachlorodibenzo-p-dioxin. The presence of operative metabolite-detoxifying pathways was also assayed. Enzymatic treatment of water-soluble metabolites with beta-glucuronidase or arylsulfatase revealed that neither glucuronic acid conjugates nor sulfate ester derivatives were present. These data, therefore, provide direct evidence that late preimplantation mouse embryos (day 3 1/2 of gestation) are similar to later developmental stages in having the enzymatic capability for xenobiotic activation and enzyme induction but are dissimilar with respect to their detoxification mechanism(s). Moreover, the ability of preimplantation embryos to activate directly polynuclear aromatic hydrocarbon to bioreactive intermediates may be of importance in assessing the ontological susceptibility of the developing embryo to carcinogenic or teratogenic chemicals. (Author abstract) (27 Refs)

ALTERATION OF OTHER CARCINOGEN-METABOLIZING ENZYMES BY CARCINOGENS

42. CORRELATIONS AMONG THE CHANGES IN HEPATIC MICROSOMAL COMPONENTS AFTER INTOXICATION WITH ALKYL HALIDES AND OTHER HEPATOTOXINS.

Moody DE, James JL, Clawson GA, Smuckler EA
Dept. Pathology, Univ. California Sch. Medicine, San Francisco, CA, 94143
Mol Pharmacol; 20(3):685-693 1981

Male Sprague-Dawley rats were treated with 13 alkyl halides (carbon tetrachloride, bromotrichloromethane, chloroform, bromoform, dichloromethane, dibromomethane, 1,2-dichloroethane, 1,2-dibromomethane, 1-bromo-2-chloroethane, 1,1,2-trichloroethane, 1,2,3-trichloropropane, 1,2-dibromo-3-chloropropane, and 1,2-epoxy-3-chloropropane) and 4 other hepatotoxins (dimethylnitrosamine (DMN), thioacetamide, ethionine, and cadmium acetate) and the content of several microsomal components was assayed. O nly two of the treatments, CCl4 and CBrCl3, resulted in measurable peroxidation of microsomal lipids. These compounds also caused significant decreases in microsomal protein, phospholipid, cytochrome P-450, cytochrome b5, NADPH cytochrome c reductase, stearic acid, and arachidonic acid within 18 hr of treatment. The other alkyl halides tested have higher halocarbon bond-dissociation energies and would be less likely to be metabolized via homolytic cleavage of the halocarbon bonds, which is associated with lipid peroxidation. DMN also had widespread effects on microsomal components but caused no peroxidation of microsomal fatty acids or loss of phospholipid, whereas a significantly lower amount of RNA was recovered from the microsomes. Microsomal responses to the majority of the compounds showed two major similarities: a significant decrease in cytochrome P-450 and a shift in the composition of microsomal fatty acid, primarily characterized by a decrease in arachidonic acid and an increase in linoleic acid. (35 Refs)

43. THE EFFECT OF 3-METHYLCHOLANTHRENE AND 3-METHYLCHOLANTHRENE PLUS PIRACETAM ON THE GAMMA-AMINOBUTYRIC ACID (GABA) CONTENT OF SEVERAL CEREBRAL REGIONS.

von Metzler A, Nitsch C
Max-Planck-Institut fur Hirnforschung, D-6000 Frankfurt a. M., W. Germany
J Cancer Res Clin Oncol; 101(3):339-343 1981

The effects of piracetam (PA) on elevation of gamma-aminobutyric acid (GABA) in cerebral regions of female Wistar rats by 3-methylcholanthrene (3-MC) were studied. Groups of rats were treated variously with PA (100 mg/kg body wt/administration, delivered by stomach tube), 3-MC (6 mg/kg body wt/administration, sc), or combinations of both. Total doses and timing of treatments varied. Treatment with 3-MC produced a rapid elevation of GABA in the hypothalamus and a more delayed elevation in the hippocampus. Walker's carcinoma also produced elevated GABA in these regions. PA alone did not affect GABA levels. Short-term PA treatment did not reduce GABA levels elevated by 3-MC, but chronic PA treatment reduced GABA to the lowest levels of any of the experimental conditions. PA was specific for the CNS and did not affect peripheral areas. Amino oxyacetic acid, which inhibits GABA-transaminase, caused elevated GABA levels in the brain and apparently increased tumor rates in rats treated with 3-MC. Although only 3-MC and PA were tested, results suggest a relationship between CNS effects and peripheral carcinogenesis. (13 Refs) (In GER)

44. EXCESSIVE ACCUMULATION OF AUTOFLUORESCENT LIPOFUSCIN IN THE LIVER DURING HEPATOCARCINOGENESIS BY METHYL CLOFENAPATE AND OTHER HYPOLIPIDEMIC PEROXISOME PROLIFERATORS.

Reddy JK, Lalwani ND, Reddy MK, Qureshi SA
Dept. Pathology, Northwestern Univ. Medical Sch., 303 East Chicago Ave., Chicago, IL, 60611
Cancer Res; 42(1):259-266 1982

Several hypolipidemic drugs and certain industrial plasticizers induce proliferation of peroxisomes and enhance the activities of peroxisome-associated enzymes in the livers of rodents. Evidence now suggests that potent hepatic peroxisome proliferators as a class are carcinogenic, although they do not appear to be mutagenic in the Salmonella-microsome assay system. We now report that long-term administration of methyl-2-[4-(p-chlorophenyl)phenoxy]-2 methylpropionate, a potent hepatic peroxisome proliferator, at a dietary concentration of 0.1% (w/w), induced hepatocellular carcinomas in 14 of 14 male F344 rats between 65 and 75 wk. The tumor cells contained several peroxisomes. Consistent with this observation was the finding of increased levels of carnitine acetyltransferase, heat-labile peroxisomal enoyl coenzyme hydratase, and peroxisomal beta-oxidation system in the tumors. As expected, methyl clofenapate was not mutagenic in the Salmonella-microsome assay using Salmonella typhimurium strains TA98 and TA100. Abundant accumulation of autofluorescent lipofuscin in the nontumorous portions of liver in rats bearing methyl-2-[4-(p-chlorophenyl)phenoxy]-2-methylpropionate induced hepatocellular carcinomas was observed. The examination in this study of livers of rats bearing hepatocellular carcinomas induced previously by five other hypolipidemic peroxisome proliferators provided retrospective evidence for increased accumulation of autofluorescent pigment in the liver cells. It is suggested that accumulation of lipofuscin in the livers of rats fed peroxisome proliferators serves as evidence for the increased production of biologically damaging free radicals as a result of H2O2 generated by sustained proliferation of peroxisomes. the hypothesis that persistent proliferation of peroxisomes and increase in peroxisomal beta-oxidation system initiates the neoplastic transformation of liver cells by increasing the intracellular production of DNA-damaging H2O2 and other reactive oxygen intermediates (OH-, O2-, 1O2) remains to be tested. (Author abstract) (49 Refs)

45. RAPID INDUCTION OF GAMMA-GLUTAMYL TRANSPEPTIDASE-RICH INTRAEPITHELIAL CLONES IN 7,12-DIMETHYLBENZ(A)ANTHRACENE-TREATED HAMSTER BUCCAL POUCH.

Solt DB, Shklar G

Dept. Oral Medicine and Oral Pathology, Harvard Sch. Dental Medicine, Boston, MA, 02115

Cancer Res; 42(1):285-291 1982

Individual gamma-glutamyl transpeptidase (GGT)-stained cells and cell doublets were rapidly induced in the epithelium of hamster buccal pouch treated with biweekly topical applications of 0.5% 7,12-dimethylbenz(a)anthracene (DMBA) in mineral oil. The cells were detected histochemically in whole mounts of pouch epithelium harvested as early as 3 days after the first application of this carcinogen. During 3 consecutive wk of DMBA treatment, progressively larger GGT-stained epithelial cell populations (plaques) up to 0.5 mm in diameter were encountered. Similar GGT-stained lesions were not detected in whole mounts of untreated epithelium and were rarely seen in GGT-stained whole mounts prepared from mineral oil-treated pouch epithelium. In an experiment designed to assess the stability of the GGT-staining pattern, very few plaques could be detected 12 wk after a 3-wk regimen of six DMBA applications. However, data are presented suggesting that a brief series of three DMBA applications reinduced GGT histochemical activity in occult intraepithelial plaques, which had lost enzyme activity but had persisted over an 11-wk treatment-free interval. The clonal nature of the GGT-stained plaques and their apparent ability to persist in an occult form for several wk or mo lend further support to the hypothesis that these carcinogen-altered cell populations may be potential precursors for the development of squamous epithelial neoplasia. (Author abstract) (40 Refs)

46. GAMMA-GLUTAMYLTRANSPEPTIDASE: A TUMOR CELL MARKER WITH A PHARMACOLOGIC FUNCTION.

Vanderlaan M, Phares W

Biomedical Sciences Div., Lawrence Livermore Natl. Lab., P.O. Box 5507, Livermore, CA, 94550

Histochem J; 13(5):865-877 1981

The histochemical distribution of gamma-glutamyltranspeptidase (GGTP) in rat and human tissues is reviewed, and the changes observed during embryogenesis and carcinogenesis are discussed. The pattern of GGTP distribution is similar in both species, with activity in adults found primarily in the proximal tubules of the kidney, the secretory follicle cells of the pancreas, and the villous cells of th jejunum. There is only minimal activity in intestinal crypt cells, but considerable in mature villus cells. Mammary gland, bile duct cells in adult liver, endothelial cells of brain capillaries, follicle sheath cells in actively growing hairs, and lymphocytes also have associated GGTP activity. Higher activity is seen in both embryonal and cancerous tissues. Soon after initial exposure to carcinogens, islands of presumably preneoplastic cells form in the liver, and are characterized by very high GGTP activity. The majority of hyperplastic nodules and carcinomas that eventually develop also have increased GGTP activity. This induction of increased activity persists long after carcinogen exposure. The possible metabolic significance of GGTP is discussed. (63 Refs)

REVIEWS AND OTHER RELEVANT STUDIES

47. SAFROLE: ITS METABOLISM CARCINOGENICITY AND INTERACTIONS WITH CYTOCHROME P-450.

Ioannides C, Delaforge M, Parke DV

Dept. Biochemistry, Univ. Surrey, Guildford, Surrey GU2 5XH, England

Food Cosmet Toxicol; 19(5):657-666 1981

This review of safrole metabolism is aimed at elucidating the importance of the allyl moiety and the methylenedioxy group in the mechanism of carcinogenesis. It includes studies concerning safrole carcinogenicity, interactions of safrole with cytochrome P-450, inhibition of mixed-function oxidase activity by safrole, ligand complex formation with cytochromes P-450 and P-448, and hemoprotein formation by safrole and isosafrole. Ligand complexing and covalent binding of reactive intermediates with the heme and protein moieties, respectively, of cytochrome P-450, may be fundamental to the mechanism of safrole carcinogenesis. Structural and functional properties of the cytochrome are substantially changed by this binding, which, since ribosomes are attached to the endoplasmic reticulum at cytochrome P-450, may be associated with loss of ribosomes known to occur following treatment with safrole or other carcinogens. Chemical carcinogenesis is associated with increases in hepatic cytochrome P-448 and simultaneous loss of cytochrome P-450 activity and could, through loss of ribosomes, result in impairment of glycoprotein synthesis and thus contribute to malignant transformation by epigenetic mechanism. Therefore, of the two functional groups of safrole, the allyl group has been shown to be associated with mutagenicity, and the methylenedioxy moiety to be associated with changes to cytochrome P-450 and possibly with epigenetic aspects of carcinogenicity. (84 Refs)

48. CHEMICAL CARCINOGENESIS.

Farber E
Dept. Pathology, Univ. Toronto, 100 College St., Toronto, ON M5G 1L5, Canada
N Engl J Med; 305(23):1379-1389 1981

Fundamental concepts related to the causation, prevention, and therapy of cancer in humans are reviewed, with emphasis on mechanistic aspects. Topics include cancer as a chronic multistage process, initiators and initiation (initiators, activation and metabolism of procarcinogens, possible molecular targets for ultimate carcinogens, DNA repair, carcinogen metabolism in human tissues, initiation), promoters and promotion (promoters, promotion, subsequent steps - progression and transfection, diet and carcinogenesis, chemotherapy and carcinogenesis), and new bioassays for carcinogens and promoters. Illustrations of (1) the current view on activation of benzo(a)pyrene to benzo(a)pyrene 7,8 dihydrodiol,9,10 epoxide, (2) sites of interactions of activated forms of carcinogens with the four DNA bases, and (3) steps in the initiation of carcinogenesis with chemicals are presented. Later phases of chemical carcinogenesis, ie post-initiation phenomena including promotion, and the relative quantitative importance of exogenous or endogenous chemical carcinogens in patients with cancer not related to smoking are not sufficiently understood. (118 Refs)

49. TUMORIGENICITY OF BAY-REGION DIOL-EPOXIDES AND OTHER BENZO-RING DERIVATIVES OF DIBENZO(A,H)PYRENE AND DIBENZO(A,I)PYRENE ON MOUSE SKIN AND IN NEWBORN MICE.

Chang RL, Levin W, Wood AW, Lehr RE, Kumar S, Yagi H, Jerina DM, Conney AH
Dept. Biochemistry and Drug Metabolism, Hoffman-La Roche, Inc., Nutley, NJ, 07110
Cancer Res; 42(1):25-29 1982

Dibenzo(a,h)pyrene [DB(a,h)P], dibenzo(a,i)pyrene [DB(a,i)P], and seven of their benzo-ring derivatives were tested for tumorigenic activity on mouse skin and in newborn mice. In the tumor studies on mouse skin, a single topical application of 50, 200, or 600 nmol of compound was followed 7 days later by twice-weekly applications of the tumor promoter 12-O-tetradecanoylphorbol-13-acetate for 16 or 24 wk. With the exception of 2,10-difluorodibenzo(a,i)pyrene, all of the compounds had significant tumor-initiating activity at all doses tested. trans-1,2-Dihydroxy-1,2-dihydrodibenzo(a,h)pyrene and trans-3,4-dihydroxy-3,4-dihydrodibenzo(a,i)pyrene, the metabolic precursors of bay-region diol-epoxides, had tumor-initiating activity that was equivalent to their parent hydrocarbons. Saturation of the double bond in the benzo-ring of these dihydrodiols resulted in the formation of tetrahydrodiols whose tumor-initiating activity was not significantly different from that observed with the corresponding dihydrodiols at the 50-nmol dose. The bay-region diol-epoxides of DB(a,h)P and DB(a,i)P, in which the benzylic hydroxyl group and the oxirane oxygen are trans (Isomer 2), induced significantly fewer tumors per mouse than did their dihydrodiol and parent hydrocarbon precursors. In the tumorigenicity study in newborn mice, a total dose of 87.5 nmol of the hydrocarbon divided into three ip injections was administered on the 1st, 8th, and 15th day of life, and tumorigenic activity was determined when the mice were 49 to 54 wk old. trans-1,2-Dihydroxy-1,2-dihydrodibenzo(a,h)pyrene and trans-3,4-dihydroxy-3,4-dihydrodibenzo(a,i)pyrene induced three- to eight-fold more pulmonary tumors per mouse and four- to five-fold more hepatic tumors per male mouse than the respective parent hydrocarbons. The corresponding tetrahydrodiols had no more than one-eighth of the pulmonary tumorigenic activity of the corresponding dihydrodiol. The bay-region diol-epoxide (Isomer 2) of DB(a,h)P had tumorigenic activity equal to the parent hydrocarbon but significantly less than its dihydrodiol precursor. The bay-region diol-epoxide (Isomer2) of DB(a,i)P was highly toxic, and only 19% of the mice survived to termination of the study. This diol-epoxide had significantly less tumorigenic activity towards the lung than did either its dihydrodiol precursor or the parent hydrocarbon. Notably, 20% of the surviving mice treated with the diol-epoxide of DB(a,i)P had leukemia at the termination of the study. 2,10-Difluorodibenzo(a,i)pyrene had no tumorigenic activity in newborn mice at the single dose tested. These results are discussed in relationship to the bay-region theory of polycyclic aromatic hydrocarbon carcinogenicity. (Author abstract) (27 Refs)

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1. CHEMICAL CARCINOGENESIS.
Farber E
Dept. Pathology, Univ. Toronto, 100 College St., Toronto, ON M5G 1L5, Canada
N Engl J Med; 305(23):1379-1389 1981

2. N-HEXANE AND ITS TOXICOLOGIC EFFECTS. A REVIEW.
Jorgensen NK, Cohr KH
Harevaenget 44, DK-4200 Slagelse, Denmark
Scand J Work Environ Health; 7(3):157-168 1981

3. SAFROLE: ITS METABOLISM CARCINOGENICITY AND INTERACTIONS WITH CYTOCHROME P-450.
Ioannides C, Delaforge M, Parke DV
Dept. Biochemistry, Univ. Surrey, Guildford, Surrey GU2 5XH, England
Food Cosmet Toxicol; 19(5):657-666 1981

RADIATION CARCINOGENESIS

4. CARCINOGENIC, MUTAGENIC, TERATOGENIC WORKSHOP.
Suit H, Hall E, Frei E
Dept. Radiation Medicine, Massachusetts General Hosp., Boston, MA, 02114
Cancer Clin Trials; 4(Suppl):37-41 1981

5. DOSIMETRY OF THE ATOMIC BOMB SURVIVORS.
Sinclair WK, Failla P, Bond VP, Loewe WE, Kerr GD, Auxier J, Wyckoff OH, Maruyama T, Schull JW, Land EC, Dobson LR, Mays WC, Seymour J
Argonne Natl. Lab., 9700 South Cass Ave., Argonne, IL, 60439
Radiat Res; 88(3):437-447 1981

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Muller E, Rickenbach M
Institut fur Sozial- und Praventivmedizin, Universitat Zurich, Gloriastrasse 32 B, 8006 Zurich, Switzerland
Praxis; 70(43):1903-1912 1981
In GER

7. FLAVONOIDS, MUTAGENS, AND CITRUS.
Horowitz RM
U. S. Dept. Agriculture, Agricultural Res. Service, Fruit and Vegetable Chemistry Lab., Pasadena, CA, 91106
ACS Symp Ser; 170:43-59 1981

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8. ETIOLOGICAL CONCEPTS IN CERVICAL CARCINOGENESIS.
Kessler II
Dept. Epidemiology and Preventive Medicine, Univ. Maryland Sch. Medicine, 655 West Baltimore St., Baltimore, MD, 21201
Gynecol Oncol; 12(2,part2):S7-S24 1981

9. CURRENT CONCEPTS ON THE AETIO-PATHOGENESIS OF ACUTE LEUKAEMIA.
Torres A, Martinez Guibelalde F, Gomez Garcia P, Garcia Castellano JM, Manzanares Escribano MR
Jefe Servicio Hematologia, Ciudad Sanitaria 'Reina Sofia' de la Seguridad Social, Cordoba, Spain
Sangre (Barc); 26(5B):700-717 1981
In SPA

10. CANCER FAMILY SYNDROME.
Svendsen LB, Bulow S
Kirurgisk-gastroenterologisk afdeling, Bispebjerg hospital, Copenhagen, Denmark
Ugeskr Laeger; 143(42):2713-2716 1981
In DAN

11. GENETIC AND BIOCHEMICAL STUDIES WITH ATAXIA TELANGIECTASIA.
Huang PC, Sheridan RB
Dept. Biochemistry, Sch. Hygiene and Public Health, Johns Hopkins Univ., Baltimore, MD, 21205
Hum Genet; 59(1):1-9 1981

ENVIRONMENTAL AND OCCUPATIONAL FACTORS IN CARCINOGENESIS

12. THE HEALTH EFFECTS AND ECOLOGICAL SIGNIFICANCE OF CHLORINE RESIDUALS IN WATER.
Kalmaz EV, Kalmaz GD
Univ. Tennessee, Univ. Station 8163, Knoxville, TN, 37916
Chemosphere; 10(10):1163-1175 1981

13. CHEMICAL AND ENVIRONMENTAL AGENTS IN GASTROINTESTINAL CARCINOGENESIS.
Deschner EE, De Cosse JJ, Sherlock P
Lab. Digestive Tract Carcinogenesis, Memorial Sloan-Kettering Cancer Center, 1275 York Ave., New York, NY, 10021
Clin Gastroenterol; 10(3):755-771 1981

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14. THE REPAIR OF DNA DAMAGE: RECENT DEVELOPMENTS AND NEW INSIGHTS.
Friedberg EC, Bonura T, Love JD, McMillan S, Radany EH, Schultz RA
Dept. Pathology, Lab. Experimental Oncology, Stanford Univ., Stanford, CA, 94305
J Supramol Struct Cell Biochem; 16(1):91-103 1981

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15. ROLE OF HORMONES INCLUDING DIETHYLSTILBESTROL (DES) IN THE PATHOGENESIS OF CERVICAL AND VAGINAL INTRAEPITHELIAL NEOPLASIA.
Robboy SJ, Truslow GY, Anton J, Richart RM
Dept. Pathology, Massachusetts General Hosp., Boston, MA, 02114
Gynecol Oncol; 12(2,part2):S98-S110 1981

16. PROSTAGLANDINS AND CANCER: A REVIEW OF TUMOR INITIATION THROUGH TUMOR METASTASIS.
Honn KV, Bockman RS, Marnett LJ
Dept. Biological Sciences, Wayne State Univ., Detroit, MI, 48202
Prostaglandins; 21(5):833-864 1981

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Rapp F, Jenkins FJ
Dept. Microbiology, Pennsylvania State Univ. Coll. Medicine, Hershey, PA, 17033
Gynecol Oncol; 12(2,part2):S25-S41 1981

18. VIRUS PAPILLOMAS IN HUMANS.
Nasemann T
Univ.-Hautklinik Eppendorf, Martinistr. 52, D-2000 Hamburg 20, W. Germany
Hautarzt; 32(11):601-606 1981
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METABOLIC ACTIVATION OF CARCINOGENS

1. POLYCYCLIC HYDROCARBON METABOLISM: A PLETHORA OF PHENOMENA.

Estabrook RW, Saeki Y, Chacos N, Capdevila J, Prough RA
Dept. Biochemistry, Univ. Texas Health Science Center at Dallas, Dallas, TX, 75235
Adv Enzyme Regul; 19:3-17 1981

Studies of benzo(a)pyrene metabolism by liver microsomes have revealed a complex pattern of products formed. The distribution of products generated depends on the types of cytochromes P-450 present and the mechanism of oxidation reactions catalyzed. It is proposed that cytochrome P-450 may function to catalyze the oxidation of benzo(a)pyrene not only by a NADPH-dependent monooxygenation type reaction, but also concomitantly by a peroxidatic type reaction. In particular, attention is directed to the role of the latter type of reaction for the formation of benzo(a)pyrene quinones. The pathways for the metabolic generation of quinones, as well as the reactivity of hydroquinones with oxygen, provide additional pathways for the formation of highly reactive, toxic products which may contribute to the alterations of cellular characteristics that result in either tumor growth or cell death. (Author abstract) (43 Refs)

2. INTERTISSUE VARIATION IN BENZO(A)PYRENE METABOLISM BY HUMAN SKIN, LUNG AND LIVER IN VITRO.

Milo GE, Trewyn RW, Tejwani R, Oldham JW, Douglas WH
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Aerosp Med Biol; (224):173 1981

An environmental agent, benzo(a)pyrene (B(a)P), is shown to transform human skin fibroblasts in vitro. This fossil fuel combustion product and other polynuclear hydrocarbons have exhibited a requirement to be biotransformed to their ultimate carcinogenic forms to induce transformation. B(a)P diol-epoxides are the most cited candidates as ultimate carcinogens. Results suggest that either the ultimate form of the carcinogen is different for fibroblasts and epithelial cells or the quantitative generation of hydroxylated metabolites is not required for neoplastic transformation in fibroblast cells. If hydroxylation is required, then the site of hydroxylation may be the significant factor. Present evidence suggests that in B(a)P treated fibroblasts the activation of B(a)P in the cell takes place other than in the microsomal P450 complex, presumably in the nucleus. (Author abstract) (no Refs)

3. COMPARATIVE METABOLISM OF 7,12-DIMETHYLBENZ(A)ANTHRACENE AND SEVERAL FLUORINATED ANALOGUES IN SYRIAN HAMSTER EMBRYO CELL CULTURE AND IN SPRAGUE-DAWLEY AND LONG-EVANS RATS IN VIVO.

Oravec CT
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Diss Abstr Int [B]; 42(5):1844-B 1981

The metabolities resulting from the rat liver microsomal oxidation of 7-12,dimethylbenz(a)anthracene (DMBA) and its fluoro analogs were compared to the metabolites from treatment of Syrian hamster embryo (SHE) cell cultures with [3H]DMBA, [3H]2F-DMBA, [14C]5F-DMBA and [3H]11F-DMBA, SHE cells in culture were exposed to each of the above DMBA analogs up to 24 hr and the metabolites both within and outside the cell (in the media) were isolated and analyzed by high pressure liquid chromatography and fluorescence spectroscopy. Metabolites were also separated into their free and conjugated components by alumina chromatography and treated with either B-glucuronidase or sulfatase enzymes to identify their conjugated components. These studies were subsequently compared to the in vivo analysis of DMBA and 2F-DMBA in Sprague-Daw ley and Long-Evans fifty day old, female rats. These two strains were chosen because of their sensitivity and resistance, respectively, to assult by DMBA and the subsequent development of mammary tumors. The DMBA and 2F-DMBA metabolites isolated from the urine of these rats were analyzed using similar techniques as those described above for the SHE cell metabolism. Several differences between the two species were noted. (no Refs)

4. CYTOTOXIC EFFECTS AND METABOLISM OF BENZO[A]PYRENE AND 7,12-DIMETHYLBENZ[A]ANTHRACENE IN DUODENAL AND ILEAL EPITHELIAL CELL CULTURES.

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JNCI; 67(6):1353-1362 1981

Two epithelial cell lines have been established from the duodenum (IEC-17) and the ileum (IEC-18) of outbred germ-free Crl:CD(SD)GN rats. They have a very similar morphology and ultrastructure, a normal rat diploid karyotype, comparable growth rates, and a similar set of surface antigens as detected with monoclonal antibodies specific for intestinal epithelial cell surface proteins in vivo. Both cell lines do not grow in soft agar and when injected into syngeneic animals do not form tumors. The toxic effects of benzo[a]pyrene (BP) and 7,12-dimethylbenz[a]anthracene (DMBA) were studied in these two cell lines. The IEC-18 cells were found to be much more sensitive to both chemicals than the IEC-17 cells. In particular, at concentrations greater than 1 ug/ml, DMBA completely and irreversibly inhibited cell proliferation in the IEC-18 cells, whereas it produced a less marked and reversible inhibition in the IEC-17 cells. The metabolism of BP and DMBA to water-soluble products was studied; BP was apparently metabolized at similar rates in the two cell lines, whereas a striking difference was observed with DMBA, which was metabolized at a rate 10-15x greater in the IEC-18 cells than that in the IEC-17 cells. These results suggest that cultured cell lines derived from different portions of the intestinal tract have similar properties in vitro, but they may have very different responses to chemical carcinogens. (Author abstract) (34 Refs)

5. ELECTROSTATIC MOLECULAR POTENTIAL CONTOUR MAPS GENERATED FROM AB INITIO MODPOT/VRDDO/MERGE WAVE FUNCTIONS OF CARCINOGENIC 3-METHYLCHOLANTHRENE AND ITS METABOLITES.

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Int J Quantum Chem; 20(5):1083-1095 1981

Electrostatic molecular potential contour maps were calculated for 3-methylcholanthrene (3-MCA), its metabolites 3-MCA 7,8-oxide and 3-MCA 9,10 oxide, and the stereoisomers 3-MCA 9,10-dihydrodiol-7,8-epoxide A beta beta beta and 3-MCA 9,10-dihydrodiol-7,8-epoxide A alpha beta alpha. Results show that the electrostatic molecular potential contour maps may be used to indicate favored positions of at tack for electrophilic species, such as 'electrophilic' oxygen to form an epoxide as well as for positive ion attack; maps for 3-MCA indicate the favored site for attack and pathways. The maps around 3-MCA 9,10-oxide and 3-MCA 9,10-dihydrodiol-7,8-epoxide indicate the directional preferences for proton assisted epoxide ring opening. By convention, atoms below the plane of the remaining rings of 3-MCA are shown on the maps as dotted, while atoms above the plane are shown as dashed. Maps around the 3-MCA dihydrodiols indicate that for certain stereoisomers the 'electrophilic' oxygen will prefer to attack from below, but for other isomers the oxygen will attack from above. Mapping provides insight into stereochemical preference for formation of different 3-MCA 9,10-dihydrodiol-7,8-epoxides. (20 Refs)

6. PATHOGENESIS OF LUNG TUMORS INDUCED BY N-NITROSOHEPTAMETHYLENEIMINE IN F344 RATS.

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Virchows Arch [Pathol Anat]; 393(3):333-343 1981

Male F344 rats were given 3 mg N-nitrosoheptamethyleneimine (NHMI) per 100 g in olive oil by gavage twice a wk for a max of 20 wk. They were killed at predetermined intervals after the start of treatment and the sequential development of NHMI-induced squamous carcinomas in the lungs was followed by light and electron microscopy. Hypertrophy of the endoplasmic reticulum in mucous and Clara cells seen in an initial study suggested that these cells were involved in metabolic activation of the nitrosamine. Basal cells were identified as the cell type that later responded by proliferation, hyperplasia, and squamous metaplasia. Only in the bronchioles, where basal cells are not found in the healthy rat, did these lesions progress further to form squamous cell carcinomas. (Author abstract) (13 Refs)

7. METABOLIC FATE OF ASYMMETRIC N,N-DIALKYLNITROSAMINES HAVING A BUTYL GROUP IN THE RAT.

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Gan; 72(6):910-920 1981

The metabolic fate of N-alkyl-N-butylnitrosamines (alkyl=ethyl, propyl, and pentyl), which induce tumors in the liver and esophagus but do not induce bladder tumors, was investigated in the rat, in order to elucidate any possible correlation between metabolism and the noncarcinogenicity to the urinary bladder of these N-nitrosamines. They were extensively metabolized in the rat, no unchanged compounds being found in the urine. The metabolic pattern of these N-nitrosamines having a butyl chain was essentially similar to that of N,N-dibutylnitrosamine, which induces tumors in the bladder as well as in the liver and esophagus. They were mainly metabolized via omega-oxidation followed by beta-oxidation and/or (omega-1)-oxidation of either of the two alkyl chains. Thus the N-alkyl-N-(3-carboxypropyl)nitrosamine and/or the N-alkyl-N-(2-carboxyethyl)nitrosamine were identified as the principal urinary metabolites. Possible important factors concerned with the induction of bladder tumors by N,N-dialkylnitrosamines are discussed from the metabolic point of view. (Author abstract) (21 Refs)

8. A CHROMATOGRAPHIC TECHNIQUE FOR THE ANALYSIS OF OXIDIZED METABOLITES: APPLICATION TO CARCINOGENIC N-HYDROXYARYLAMINES IN URINE.

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Anal Biochem; 118(1):120-125 1981

A new chromatographic detection method for oxidized metabolites has been developed based on the reaction of eluted compounds with an Fe+++-bathophenanthroline colorimetric reagent in a postcolumn reactor. The method is sensitive to N-hydroxyarylamines, aryldiamines, phenolic amines, and ascorbic acid. It has been applied to the analysis of toxic N-oxidized metabolites in rhesus monkey urine after the animals were dosed with the bladder carcinogens, 1-and 2-napthylamine. These compounds are oxidized to the corresponding N-hydroxyarylamines in the liver, conjugated at the N-glucuronide, and excreted in the urine. The N-glucuronide has been shown to undergo acidic hydrolysis in the urine to release the free N-hydroxyarylamine, an ultimate carcinogen for the induction of bladder tumors. In this study, the N-hydroxy-N-glucuronide of 2-naphthylamine was found to be excreted at the rate that was 6.8x that of the 1-naphthylamine isomer. This is consistent with the much higher carcinogenic potency of 2-naphthylamine in a variety of species. (Author abstract) (18 Refs)

9. METABOLIC ACTIVATION AND CYTOTOXICITY OF CYCLOPHOSPHAMIDE IN PRIMARY CULTURES OF POSTNATAL RAT HEPATOCYTES.

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Biochem Pharmacol; 30(23):3225-3230 1981

We have developed a model of primary cultures of postnatal rat hepatocytes to characterize the metabolic activation of xenobiotics to toxic intermediates and to study the mechanism(s) by which these chemicals produce cellular injury. This model was employed to investigate the cytochrome P-450 mediated biotransformation of cyclophosphamide (CP) to cytotoxic metabolites that nonspecifically alkylate DNA and cellular proteins. The parenchymal cells were isolated by an in situ collagenase perfusion technique and cultured for 24 hr prior to drug treatment. The cultures were then exposed to CP concentrations ranging from 1 x 10(-4) M to 1 x 10(-3) M for 24 hr. Initial studies indicated minimal toxicity to non-replicating parenchymal hepatocytes maintained in ornithine-supplemented, arginine-deficient medium. The addition of arginine permitted the overgrowth of fibroblasts in the same culture system. These fibroblasts then became the target of alkylating CP metabolites produced by the parenchymal cells. By day 3 after CP administration, cell number and total protein per dish decreased by over 40%. The morphology of the cultures changed dramatically because of fibroblast destruction. The cytotoxicity to dividing fibroblasts was eliminated by administering 2-diethylaminoethyl-2,2-diphenylvalerate hydrochloride (SKF 525-A), an inhibitor of the cytochrome P-450 monooxygenase system, to the co-cultures treated with CP. The alkylating metabolites of CP produced by parenchymal cells and released into the culture medium were quantitated by reacting aliquots of medium from CP-treated cells with 4-(p-nitrobenzyl)pyridine. These results provide both direct and indirect evidence of drug metabolism in cultured cells and suggest that this co-culture system can be utilized to evaluate the metabolic activation of xenobiotics. (Author abstract) (49 Refs)

10. STUDIES ON THE MECHANISM OF METABOLIC ACTIVATION OF FTORAFUR (R,S-1-(TETRAHYDRO-2-FURANYL)-5-FLUOROURACIL) TO 5-FLUOROURACIL.

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Diss Abstr Int [B]; 42(5):1903-B 1981

We have studied the metabolism, pharmacokinetics, enzyme systems responsible for the activation, and the extent of conversions of ftorafur (FT). We have developed high pressure liquid chromatographic assays and gas chromatographic assays to study the pharmacokinetics and metabolism of FT in animals and patients. The disposition of FT in rats, rabbits, and humans followed two compartment kinetics with mean beta phase half-lives of 5, 2, and 9 hr, respectively. Plasma concentrations of FU in FT-treated animals and patients were exceedingly low. Seven FT metabolites have been identified in plasma and urine samples of experimental animals and humans. A few metabolic activation pathways of FT to FU have been established. One of the major activation pathways of FT in rabbits and humans is mediated by the soluble enzymes in liver homogenates, and is not dependent on the hepatic microsomal cytochrome P-450 enzymes. Pharmacokinetic analysis of the plasma concentrations of FT and FU indicate that the conversion of FT to FU may also occur in target tissues, and the FU generated would be further metabolized without redistributing into the general circulation due to its rapid intracellular metabolism. This is consistent with the observed antitumor activity of FT in spite of the exceedingly low plasma concentrations of FU, and is further supported by the finding that the major metabolic activation pathway of FT to FU is mediated by soluble enzymes. (no Refs)

OTHER METABOLISM OF CARCINOGENS

11. CONJUGATION PATHWAYS IN HUMAN BRONCHIAL CARCINOMA CELL LINES.

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Biochem Pharmacol; 30(24):3333-3336 1981

Human bronchial carcinoma cell lines in monolayer cell culture were used to study the conjugation of 1-naphthol and 3-hydroxybenzo(a)pyrene, two phenolic substrates. Cell lines, able to metabolize 1-naphthol to glucuronic acid and sulfate ester conjugates, showed a predominance of glucuronidation. This is in sharp contrast to normal human peripheral lung which metabolizes these phenolic substrates predominantly to the sulfate ester conjugates. The bronchial tumor cell lines do not all have the same conjugation pattern and they differ in the metabolism of phenolic substrates when compared to normal peripheral lung. The cell lines generally show that sulfate ester conjugation was either reduced or absent. In some cases, dependent on the type of tumor the cell line was derived from, glucuronic acid conjugation was elevated. Initial sub-cellular studies with a poorly differentiated epidermoid cell line (Ben) demonstrated that this line had an active UDP-glucuronosyltransferase (Km 33 uM and Vmax 1.8 nmoles min-1.mg protein(-1)), using 1-naphthol as substrate. However, this cell line was unable to form significant amounts of sulfate ester conjugates, due to either low sulfotransferase activity, or an inability to generate adenosine 3'-phosphate 5'-sulfatophosphate (PAPS). (Author abstract) (20 Refs)

12. DISPOSITION OF THE FLAME RETARDANT, TRIS(1,3-DICHLORO-2-PROPYL) PHOSPHATE, IN THE RAT.

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Drug Metab Dispos; 9(5):434-441 1981

Distribution, metabolism, and excretion of tris(1,3-dichloro-2-propyl)phosphate (TDCP) were examined in male Sprague-Dawley rats. Five days after iv administration of 14C-TDCP, 54%, 22%, and 16% of the administered radiolabel was found in the urine, expired air, and feces, respectively; 4% was recovered in the body. TDCP was metabolized to bis(1,3-dichloro-2-propyl)phosphate (BDCP), which was the major urinary, fecal, and biliary metabolite. Other metabolites included 1,3-dichloro-2-propyl phosphate and 1,3-dichloro-2-propanol. TDCP was rapidly distributed out of plasma and into tissues. Less than 19% of administered TDCP was recovered as TDCP in the body 30 min after dosing. Rapid disappearance of TDCP was not due to excretion, as 82% of the administered radiolabel remained in the body and only traces (less than 0.1%) of the administered dose were found in the urine and feces as TDCP 30 min after dosing. Metabolism to BDCP was the major route of elimination of TDCP, whereas BDCP was eliminated primarily by excretion, with 63% of the administered phosphate (TDCP) recovered as BDCP in the urine and feces. 1,3-Dichloro-2-propan ol was mutagenic in Salmonella typhimurium TA100 without metabolic activation. TDCP was weakly mutagenic following activation with mouse phenobarbital-induced liver homogenates. Analysis of mutagenicity data on the basis of the number of revertants/umole demonstrated that TDCP was 3-20x more potent than 1,3-dichloro-2-propanol, suggesting that a metabolite other than the alcohol may be responsible for TDCP mutagenicity. Under the same conditions, BDCP and 1,3-dichloro-2-propyl phosphate were not mutagenic. (22 Refs)

MODIFICATION OF CARCINOGEN METABOLISM

13. STUDIES ON THE IN VITRO METABOLISM OF AFLATOXIN B1 AND G1 IN THE LIVER OF RATS FED AT VARIOUS LEVELS OF VITAMIN C.

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Biochem Pharmacol; 30(24):3317-3322 1981

Male and female weanling rats, divided into three groups, were maintained for 30, 60 and 90 days on an experimental diet without vitamin C. The drinking water containing or devoid of vitamin C was offered each day. The first group had no vitamin C; the second group or control had normal vitamin C and the third group had above-normal vitamin C in the water. Twenty-four hr after the last feeding, the animals were decapitated and the liver microsomes plus soluble fraction (9,000 g) were prepared. This preparation was used for O-demethylase and the hydroxylase assays of aflatoxins B1 and G1 (AFB1 and

AFG1). Results from O-demethylation in both control and experimental groups of both sexes, showed that O-demethylase activity is directly related to ascorbic acid content of the water. But the hydroxylase activity in male and female animals maintained on the same diet showed only slight differences. In the male, there was an increase with time of hydroxylase activity with AFB1 up to 60 days and a decrease at 90 days. Hydroxylation assay revealed that in the female, metabolism of AFB1 increased at 30 days but decreased at 60 and 90 days. (Author abstract) (29 Refs)

MUTAGENICITY OF ACTIVATED METABOLITES OF CARCINOGENS

14. THE INDUCTION OF SISTER-CHROMATID EXCHANGES IN CHINESE HAMSTER OVARY CELLS BY K-REGION EPOXIDES AND SOME DIHYDRODIOLS DERIVED FROM BENZ[A]ANTHRACENE, DIBENZ[A,C]ANTHRACENE AND DIBENZ[A,H]ANTHRACENE.

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Mutat Res; 84(2):389-398 1981

Benz[a]anthracene (BA), dibenz[a,c]anthracene (DB[a,c]A), dibenz[a,h]anthracene (DB[a,h]A), and some of their metabolites were studied for induction of sister chromatid exchanges (SCE) in cultured Chinese hamster ovary cells. BA and 1,2; 5,6-; 8,9-; and 10,11-diols induced some SCE, but they were not as active as either benz[a]anthracene 5,6-oxide, which induced an approx 2-fold increase in SCE at 1 ug/ml, or trans-3,4-dihydro-3,4-dihydroyxbenz[a]anthracene. Despite the strong cytotoxicity of DB[a,c]A, it did not induce SCE. However, all DB[a,c]A metabolites tested (1,2-; 3,4-; and 10,11-dihydrodiols) induced SCE in a dose-dependent manner; trans-1,2-dihydro-1,2-dihydroxybenz[a,c]anthracene (4 ug/ml) induced a greater than 4-fold increase in SCE. DB[a,h]A was only weakly active. Trans-3,4-dihydro-3,4-dihydroxydibenz[a,h]anthracene was the most active DB[a,h]A metabolite, producing a greater than 3-fold increase in SCE at 2 ug/ml. Dibenz[a,h]anthracene 5,6-oxide actively induced SCE in a dose-dependent manner, whereas the 5,6-and 1,2-diols were almost inactive. K-region 5,6-epoxides derived from BA and DB[a,h]A were more active than the parent hydrocarbon in inducing SCE. Data suggest that when activated, the three polycyclic aromatic hydrocarbons studied can be metabolized to the ultimate carcinogen in CHO cells possessing some microsomal monooxygenase. (35 Refs)

15. MUTAGENICITY AND CYTOTOXICITY OF ETHYLENE OXIDE IN THE CHO/HGPRT SYSTEM.

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Environ Mutagen; 3(6):683-686 1981

Cytotoxicity and mutagenicity of ethylene oxide (EO) in the Chinese hamster ovary cell/hypoxanthine-guanine phosphoribosyl transferase (CHO/HGPRT) system were examined. EO was found to be a direct acting mutagen and cytotoxic agent. Mutation frequency showed a linear dose response; mutagenic activity of EO was 24.7 x 10(-6) mutants/clonable cell/millimole. Compared to halogenated ethanes such as ethylene dibromide, ethylene chlorobromide, and ethylene dichloride, EO is only less mutagenic than ethylene dibromide. S9 increased the cytotoxicity of ethylene chlorobromide and ethylene 5-25x and mutagenicity 4x; cytotoxicity of ethylene dibromide remained unchanged. (20 Refs)

16. MUTAGENICITY OF URINARY METABOLITES OF BENZIDINE AND BENZIDINE-BASED AZO DYES.

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Int Arch Occup Environ Health; 49(2):177-185 1981

Mutagenicity of urinary metabolites of benzidine and benzidine-based azo dyes was studied. Mutagenicity of the urine extracts was tested in the Salmonella/mammalian-microsome assay. Results of the mutagenicity assay and gas chromatography analysis of the urine extracts suggested that the azo dyes may decompose and release benzidine. The urinary metabolites of benzidine were more mutagenic than benzidine itself. Azo dyes studied were Direct Deep Black EX and Congo Red, both containing a 4,4'-diazobiphenyl group. (23 Refs)

17. MUTAGENICITY OF 4-AMINOAZOBENZENE, N-HYDROXY-4-AMINOAZOBENZENE, 4-NITROSOAZOBENZENE, 4-NITROAZOBENZENE, AND THEIR RING METHOXYLATED DERIVATIVES ON SALMONELLA.

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Dept. Hygienic Chemistry, Pharmaceutical Inst., Tohoku Univ., Aobayama, Sendai 980, Japan
Gan; 72(6):921-929 1981

The mutagenicity of 4-aminoazobenzene (AAB), N-hydroxy-4-aminoazobenzene, 4-nitroazobenzene, and their 2-, 3-, 4'-methoxyl and 2,5-dimethoxyl derivatives, and 2-methoxy-4-nitrosoazobenzene and 3-methoxy-4-nitrosoazobenzene were examined on Salmonella typhimurium TA98 and TA100. The activities of AAB dyes upon S-9 metabolic activation were related to their carcinogenic activities in the rat. The potent carcinogen 3-methoxy-4-aminoazobenzene was a potent mutagen for both tester strains. The moderate or weak carcinogens 4'-methoxy-4-aminoazobenzene and AAB were moderate or weak mutagens for one or both of the tester strains. The noncarcinogens 2-methoxy-4-aminoazobenzene and 2,5-dimethoxy-4-aminoazobenzene were non-mutagenic. In contrast to AAB dyes, N-hydroxy-4-aminoazobenzene dyes showed greater mutagenicity than the mother AAB dyes, without S-9 treatment. 4-Nitroazobenzene dyes and 4-nitrosoazobenzene dyes showed mutagenicity without S-9 treatment, and the activities were related to those of the corresponding N-hydroxy-AAB dyes. All 4-nitroazobenzene dyes were mutagenic in the presence of S-9, suggesting the production of mutagens other than N-hydroxy-AAB dyes by the S-9 treatment. The cytotoxicity of azo dyes to bacteria had no apparent relation to the mutagenic activity of the azo dyes. Incubation of 4-nitroazobenzene dyes with TA100 bacteria yielded N-hydroxy-AAB dyes. The synthesis and properties of new N-hydroxy-AAB dyes, 4-nitroazobenzene dyes and 4-nitrosoazobenzene dyes are described. (Author abstract) (27 Refs)

18. EFFECT OF METHYL SUBSTITUTION ON MUTAGENICITY OF 2-AMINO-3-METHYLIMIDAZO[4,5-F]QUINOLINE, ISOLATED FROM BROILED SARDINE.

Nagao M, Wakabayashi K, Kasai H, Nishimura S, Sugimura T
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Carcinogenesis; 2(11):1147-1149 1981

The compound 2-Amino-3-methylimidazo[4,5-f]quinoline [I] is a potent mutagen isolated from broiled sun-dried sardine. [I] and its seven derivatives, (2 isomers, 1 demethylated derivative and 4 methyl-substituted derivatives), were tested for mutagenicity on Salmonella typhimurium TA98 and TA100 in the presence of S9 mix. 2-Amino-1,4-dimethylimidazo[4,5-f]quinoline was the strongest mutagen of these 8 compounds on TA98, giving 159,000 revertants/nmol (750,000 revertants/ug). The demethylated derivative, 2-aminoimidazo[4,5-f]-quinoline, had very weak mutagenicity, inducing only 55 revertants/nmol (200 revertants/ug). Compounds having a methyl group at position N-1 or N-3 of 2-aminoimidazo[4,5-f]quinoline were strong mutagens. The 1,5-dimethyl-derivative was more mutagenic than the 3,5-dimethyl-derivative. Introduction of a methyl group at position 4 and position 5 enhanced and reduced the mutagenicity, respectively. All the compounds tested were more mutagenic to TA98 than to TA100, but their relative orders of mutagenicity with TA98 and TA100 were the same. (Author abstract) (22 Refs)

19. PULMONARY ADENOMA RESPONSE OF STRAIN A MICE TO SULFONIC ACID DERIVATIVES OF 1-AND 2-NAPHTHYLAMINES.

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JNCI; 67(6):1299-1302 1981

Various sulfonic acid derivatives of 1-naphthylamine and 2-naphthylamine were tested in inbred A/St (male and female) mice by the pulmonary adenoma bioassay to determine if this class of compounds, used as intermediates in the dye-stuff industry, possesses tumorigenic activity. neither 1-naphthylamine nor the four sulfonic acid derivatives of 1-naphthylamine tested were tumorigenic. However, 2-naphthylamine and two of the three sulfonic acid derivatives of 2-naphthylamine tested produced statistically significant lung tumor responses at comparable doses. These results indicated that this class of compounds should be examined more extensively for carcinogenic activity. (Author abstract) (25 Refs)

20. THE GENETIC ACTIVITY OF DINITROPYRENES IN YEAST: UNUSUAL DOSE RESPONSE CURVES FOR INDUCED MITOTIC GENE CONVERSION.

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Carcinogenesis; 2(11):1201-1205 1981

The compound 1,6-Dinitropyrene (1,6DNP) and 1,8-dinitropyrene (1,8DNP) were tested for their ability to induce mitotic gene conversion at the trp 5 and his 4 loci in the yeast Saccharomyces cerevisiae JD1. Both compounds were shown to be potent inducers of gene conversion in yeast, with 1,6DNP being somewhat more active than 1,8DNP. Unusual dose-response curves were obtained in that toxicity and genetic activity decreased at the higher concentrations examined. This reduction in genetic activity may reflect a decrease in the ability of yeast cells to convert the dinitropyrenes to their mutagenic forms when the concentration of the compounds exceeds a certain level. (Author abstract) (13 Refs)

21. THE SALMONELLA MUTAGENICITY ASSAY ON FENTICONAZOLE, A NEW ANTIFUNGAL IMIDAZOLE DERIVATIVE.

Veronese M, Barzaghi A, Bertoncini A, Zadro M
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Arzneim Forsch; 31(12):2140-2142 1981

The antibacterial and antifungal imidazole derivative alpha-(2,4-dichlorophenyl)-beta,N-imidazolylethyl 4-phenylthiobenzyl ether nitrate (fenticonazole) was tested for mutagenicity in Salmonella typhimurium in the Ames test. No mutagenicity was detected in strains TA 1535, TA 1537, TA 1538, TA 98, or TA 100 with or without microsomal activation. (5 Refs)

22. MUTAGENICITY STUDIES ON FENTICONAZOLE, A NEW ANTIFUNGAL IMIDAZOLE DERIVATIVE.

Veronese M, Barzaghi D, Bertoncini A, Zadro M
Microbiology Section, Res. Div., Recordati S.p.A., Cas. Post. 10119, I-20100 Milano, Italy

Arzneim Forsch; 31(12):2142-2144 1981

The mutagenicity of alpha-(2,4-didichlorophenyl)-beta,N-imidazolylethyl 4-phenylthiobenzyl ether nitrate (fenticonazole) was tested in a forward mutational assay in Schizosaccharomyces pombe and a mitotic gene conversion assay in Saccharomyces cerevisiae. No mutagenicity was detected in either test. In vivo mammalian studies are in progress. (5 Refs)

23. INDUCTION OF SISTER CHROMATID EXCHANGES AND BACTERIAL REVERTANTS BY ORGANIC EXTRACTS OF AIRBORNE PARTICLES.

Lockard JM, Viau CJ, Lee-Stephens C, Caldwell JC, Wojciechowski JP, Enoch HG, Sabharwal PS
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Environ Mutagen; 3(6):671-681 1981

The genotoxicity of organic extracts of airborne particles collected in Lexington, Kentucky was evaluated. In sister chromatid exchange (SCE) assays conducted in human lymphocytes, extracts of all samples induced dose-related increases in number of SCEs. Concentrations of 60 or 80 ug extract/ml caused approximate doubling of background frequency of SCE, to 7.0-9.6 SCE/cell. No metabolic activation was used, indicating that compounds contained in the samples were either direct acting or activated by the lymphocytes. Addition of S9 activation induced negligible increases in number of SCEs for all samples in V79 Chinese hamster fibroblasts. Concentrations of more than 60-80 ug of the extracts were toxic to both human lympnocytes and V79 cells, inhibiting cell division and causing cell lysis. Dose related increases in number of bacterial revertants were induced by all of the organic extracts tested in the Ames assay with both TA98 and TA100. Addition of S9 caused no significant differences in reversion frequencies. (41 Refs)

BINDING OF CARCINOGENS AND THEIR METABOLITES TO MACROMOLECULES

24. METABOLISM AND BINDING OF BENZO(A)PYRENE AND 2-ACETYLAMINOFLUORENE BY SHORT-TERM ORGAN CULTURES OF HUMAN AND RAT BLADDER.

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Cancer Res; 42(2):642-648 1982

The ability of organ cultures of normal human and rat bladder to metabolize the polycyclic hydrocarbon, benzo(a)pyrene (BP), and the arylamine, 2-acetylaminofluorene, has been studied. Cultures were maintained for 0 to 6 days in a chemically defined medium before incubation with [3H]BP (0.3 to 0.5 uM) or 2-[14C]acetylaminofluorene (18 to 25 uM) for 24 hr. Ethyl acetate-soluble and water-soluble metabolites were produced from both compounds by both species. The ethyl acetate extracts from [3 H]BP-treated human cultures contained 9,10-dihydro-9,10-dihydroxybenzo(a)pyrene, 7,8-dihydro-7,8-dihydroxybenzo(a)pyrene, and 3-hydroxybenzo(a)pyrene. Rat bladder cultures produced similar metabolites but in slightly different proportions. Ethyl acetate-soluble products of 2-[14C]acetylaminofluorene from human cultures contained 7-hydroxy-2-acetylaminofluorine, 9-hydroxy-2-acetylaminofluorene, 2-aminofluorene, and N-hydroxy-2-acetylaminofluorene. Rat bladder cultures produced similar metabolites, but 2-aminofluorene was found in relatively higher proportion. Hydrolysis by beta-glucuronidase of the water-soluble products produced from both carcinogens gave ethyl acetate-extractable derivatives. These hydrolyzable glucuronide conjugates were relatively more abundant following metabolism of the carcinogens by the rat than by the human cultures. Covalent binding to DNA occurred with [3H]BP in both human (19.7 +-13 pmol/mg DNA) and rat cultures (22.8 +-8.6 pmol/mg DNA). As with other human tissues, considerable variation (50-fold) was observed between individuals. The results demonstrate that both human and rat bladder epithelium can metabolize known potent carcinogens and, in the case of BP, can effect covalent binding between the products of metabolism and the urothelial cell DNA. In theory, carcinogenesis in the urinary bladder could thus be initiated by carcinogens produced or excreted in the urine without the necessity for their prior metabolism elsewhere in the body. (Author abstract) (66 Refs)

25. STUDIES ON THE IN VITRO TRANSFER OF DNA BINDING BENZO[A]PYRENE METABOLITES FROM RAT HEPATOCYTES TO HUMAN FIBROBLASTS.

Nordenskjold M, Svensson SA, Jernstrom B, Moldeus P, Dock L, Soderball S
Dept. Clinical Genetics, Karolinska Hosp., S-104 01 Stockholm, Sweden
Carcinogenesis; 2(11):1151-1160 1981

The release and reabsorption of benzo[a]pyrene (BP) metabolites were studied in isolated rat hepatocytes incubated with BP. There was a rapid uptake of BP by the hepatocytes which was followed by an excretion of organic as well as water-soluble metabolites. Upon further incubation the BP-dihydrodiols and BP-phenols were reabsorbed by the cells and finally excreted as water-soluble conjugates. The metabolism of BP by the hepatocytes also resulted in the formation and release of reactive intermediates to the incubation medium. The DNA-binding intermediates released from the cells were consistent with trans-7,8-dihydroxy-7,8-dihydrobenzo[a]pyrene-9,10 oxide(s) and 9-hydroxybenzo[a]pyrene-4,5-oxide(s). The BP-metabolites were found to bind to hepatocyte and fibroblast DNA. The degree of DNA binding was estimated as the formation of DNA strand breaks. BP metabolites formed within the hepatocytes and transferred to the fibroblasts were found to induce DNA strand breaks in the latter cells. Addition of DNA to the medium markedly decreased the fraction of single stranded DNA in these cells. Under conditions where the excretion from hepatocytes of BP-phenols and BP-dihydrodiols were increased, the amount of DNA strand breaks in the fibroblasts increased. (Author abstract) (72 Refs)

26. COVALENT BINDING OF BENZO(A)PYRENE TO DNA IN FISH LIVER.

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Biochem Biophys Res Commun; 103(2):780-787 1981

The extent of covalent binding of benzo(a)pyrene (BaP) intermediates to hepatic DNA and protein was determined in English sole exposed po to 3H-BaP. Radioactivity in the liver represented 0.6% of the administered dose at 16 hr. The liver concentration of BaP-derived radioactivity did not change significantly from 16-336 hr after BaP administration; greater than 98% of the total radioactivity in liver was in the form of the organic solvent- and water-soluble metabolites. Detectable binding of BaP intermediates to liver DNA was observed between 6 and 336 hr after BaP exposure. No statistically significant change was observed in the binding values for DNA during the 2 wk exposure; the extent of BaP binding to liver protein did not change significantly over the 2 wk period. The av of all specific activity values for protein (58 +-51) was not significantly different from the av value for DNA (44 +-39). The results indicated that the extent of BaP binding to fish liver DNA is comparable to values reported for mammalian tissues susceptible to polycyclic aromatic hydrocarbon-induced neoplasms; chemical modification of hepatic DNA was observed for at least 2 wk after a single exposure to BaP. (30 Refs)

27. MOLECULAR BIOLOGY OF ENVIRONMENTAL AROMATIC HYDROCARBONS. PROGRESS REPORT, 1 JAN. -31 DEC. 1980.

Weiss SB
Chicago Univ., Chicago, IL
Sci Tech Aerosp Rep; 19(2):240 1981

Three different aspects of hydrocarbon action are investigated: the biochemical effect of benzo(a)pyrene-diol-epoxide on the replication of Simian virus 40; the reaction of benzo(a)pyrene-7,8-diol with viral DNA; and the effect of PAH derivatives on RNA transcription. (Author abstract) (no Refs)

28. STIMULATION OF TRANSFER OF METHYL GROUPS FROM O6-METHYLGUANINE IN DNA TO PROTEIN BY RAT LIVER EXTRACTS IN RESPONSE TO HEPATOTOXINS.

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Dept. Physiology and Specialized Cancer Res. Center, Milton S. Hershey Medical Center, Hershey, PA, 17033
Carcinogenesis; 2(11):1195-1200 1981

An enzymatic activity present in rat liver extracts catalyzes the transfer of methyl groups from O6-methylguanine in DNA to protein. This activity was stimulated by treatment of rats with thioacetamide, carbon tetrachloride, 1,2-dimethylhydrazine, diethylnitrosamine, dimethylnitrosamine and by partial hepatectomy but not by treatment with N-methyl-N-nitrosourea or streptozotocin. These results suggest that an enhancement of this activity accompanies the increase in cell division brought about by these agents and is not necessarily a specific response to the presence of alkylated bases in DNA. (Author abstract) (38 Refs)

29. CELLULAR DNA DAMAGE BY NITROSOCIMETIDINE: A COMPARISON WITH N-METHYL-N'-NITROSO-NITROSOGUANIDINE AND X-IRRADIATION.

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Chem Biol Interact; 38(1):87-98 1981

Permanently proliferating lymphoblastoid cell lines (LCLs) and normal unstimulated peripheral blood leukocytes have been used to study the effects of nitrosocimetidine (NC) on cultured human lymphoid cells. The approaches that were used to assess the cells' ability to cope with NC were: (i) determination of cell survival as measured by colony formation in microtiter plates; (ii) quantitation of DNA synthesis and DNA-repair replication by isopyknic sedimentation of DNA density labeled with 5-bromo-2-deoxyuridine (BrdU); (iii) measurement of the induction of alkali labile lesions and strand breaks by NC in 3H-labeled DNA using velocity sedimentation in alkaline sucrose. In summary, treatment with NC was found to inhibit both replicative DNA synthesis and colony formation in LCLs. At the molecular level, NC treatment induced alkali labile lesions in LCL DNA and elicited DNA-repair replication in proliferating LCLs as well as unstimulated lymphocytes. Considered in total, these data indicate that NC is reactive with human DNA in the cellular environment in a manner similar to methylating nitroso compounds which have been shown to be carcinogenic. The significance of these findings will be discussed. (Author abstract) (25 Refs)

30. A COMPARISON OF THE CARCINOGEN-DNA ADDUCTS FORMED IN RAT LIVER IN VIVO AFTER ADMINISTRATION OF SINGLE OR MULTIPLE DOSES OF N-METHYL-4-AMINOAZOBENZENE.

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(c/o Kadlubar) Div. Carcinogenesis, Food and Drug Admin., Environmental Protection Agency, Natl. Center Toxicology Res., Jefferson, AR, 72079
Chem Biol Interact; 38(1):15-27 1981

The compound N-methyl-4-aminoazobenzene (MAB) is believed to be metabolized in the liver to an electrophilic N-sulfonyloxy ester which binds covalently to cellular macromolecules, resulting in the induction of hepatic neoplasia. A single dose of MAB is not sufficient for complete carcinogenic activity, so we sought to identify the MAB-DNA adducts present in rat liver after multiple oral doses of [3H]MAB. The MAB was administered by intubation at a level of 0.2 mmol/kg for 1, 3 or 4 doses and animals were sacrificed at 8 hr after the last dose. Hepatic DNA was isolated by extraction and hydroxylapatite chromatography and was enzymatically hydrolyzed to MAB-mononucleoside adducts, which were quantitated by high pressure liquid chromatography (HPLC). After three doses, N2-dG, C8-dG, and an unknown adduct were detected. By four doses, these accounted for 51%, 25% and 23% of the total adducts. This data is consistent with rapid removal of the C8-dG derivative and the relative persistence of the N2-dG and the unknown adduct. The latter was shown to exhibit chromatographic and pH-dependent solvent partitioning properties that were identical to a product also present in DNA treated with the synthetic ultimate carcinogen, N-benzoyloxy-N-methyl-4-aminoazobenzene. Analysis of this adduct by field desorption mass spectrometry and, after perdeuteromethylation, by electron mass spectrometry, indicated the structure to be a deoxyadenosin-N6-yl derivative substituted through an aromatic ring of MAB. Further analysis of 270 MHz 1H-NMR spectroscopy allowed complete assignment of the MAB and adenyl resonances and was uniquely consistent with a 3-(deoxyadenosin-N6-yl)-MAB structure. Since this persistent adduct is potentially mutagenic due to possible tautomeric equilibria between the N6-amino and N6-imino structures, it may represent an initiating lesion in MAB hepatocarcinogenesis. (26 Refs)

31. AMINO ACID CONJUGATION OF N-HYDROXY-4-AMINOAZOBENZENE DYES: A POSSIBLE ACTIVATION PROCESS OF CARCINOGENIC 4-AMINOAZOBENZENE DYES TO THE ULTIMATE MUTAGENIC OR CARCINOGENIC METABOLITES.

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Gan; 72(6):937-943 1981

The activation process of N-hydroxy-4-aminoazobenzene (N-HO-AAB) dyes, proximate mutagenic or carcinogenic metabolites of AAB dyes, to the ultimate mutagenic or carcinogenic metabolites was studied by the use of an amino acid conjugation (aminoacylation) system catalyzed by yeast seryl-tRNA synthetase and [3H]ATP. A potent mutagen, N-hydroxy-3-methoxy-AAB (N-OH-3-MeO-AAB), as well as a non-mutagen, N-OH-2-MeO-AAB, were equally susceptible to N-O-serine conjugation. A weak mutagen, N-OH-AAB, and a moderate mutagen, N-OH-2,5-diMeO-AAB, were also susceptible to the aminoacylation, but to a lesser extent than the 2-or 3-methoxyl homologs. In contrast, N-hydroxy-N-methyl-4-aminoazobenzene and a moderate mutagen, N-OH-4'-MeO-AAB, were not susceptible to the aminoacylation. The ability of these N-OH-AAB dyes to bind with nucleic acid after serine conjugation was proportional to the susceptibility of the dyes to serine conjugation. Serine conjugates of N-OH-AAB dyes reacted with poly G, but not with poly A, poly C, or poly U, suggesting that the azo dyes selectively bind with guanine base of nucleic acids. The susceptibility of N-OH-AAB dyes to aminoacylation was compared with the carcinogenic, mutagenic and unscheduled DNA synthesis-inducing activities of these and the mother AAB dyes. (Author abstract) (29 Refs)

32. ABERRANT AND NONRANDOM METHYLATION OF CHROMOSOMAL DNA-BINDING PROTEINS OF COLONIC EPITHELIAL CELLS BY 1,2-DIMETHYLHYDRAZINE.

Boffa LC, Gruss RJ, Allfrey VG
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Cancer Res; 42(2):382-388 1982

The alkylating carcinogen 1,2-dimethylhydrazine (DMH) induces colonic tumors with high incidence. The sites of in vivo modification of target macromolecules were studied using [methyl-3H]DMH. Carcinogen binding to subcellular fractions of colonic epithelial cells was analyzed at time intervals ranging from 10 min to 36 hr, with particular emphasis on the alkylation of nuclear constituents. DMH modifies not only nucleic acids but also histones and other DNA-binding proteins in the target cells. Separation of the 3H-methylated amino acids showed aberrant methylation patterns after exposure to [3H]DMH, as compared with methylations observed with [methyl-3H]methionine as a natural methyl group donor. DMH-modified histone H1 contained methylated lysine, arginine, and histidine residues not normally found, and other histones had abnormal methylarginine contents. High-mobility-group proteins and other nuclear proteins contained methyllysine residues not normally detected. Proteins known to be associated with template-active and more accessible DNA sequences, such as the high-mobility group proteins and the multiacetylated forms of histones H3 and H4, were preferentially damaged after exposure to [3H]DMH. The result suggests that carcinogen-induced chromosomal damage is not random and may selectively affect proteins in the actively transcribing or replicating genes in the target cells. That damage affects the amino acids most likely to be involved in DNA binding. (Author abstract) (47 Refs)

33. TESTS FOR MUTAGENICITY IN SALMONELLA AND COVALENT BINDING TO DNA AND PROTEIN IN THE RAT OF THE RIOT CONTROL AGENT O-CHLOROBENZYLIDENE MALONONITRILE (CS).

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Arch Toxicol; 49(1):15-27 1981

The aim of this study was to determine whether o-chlorobenzylidene malononitrile (CS) exhibits any genotoxic activity towards Salmonella or mammalian DNA in vivo. CS was synthesized with a [14C]-label at the benzylic carbon atom. It was administered ip at a dose level of 13 mg/kg (1 mCi/kg) to young adult male rats. Liver and kidney DNA was isolated after 8, 25, and 75 hr. The radioactivity was at (liver, 8 and 75 hr) or below (all other samples) the limit of detection of 3 dpm. Therefore, a possible binding of CS to DNA is at least 10(5) times lower than that of the strong hepatocarcinogen aflatoxin B1, and 4,000x lower than that of vinyl chloride. In contrast to this lack of DNA binding, but in agreement with the chemical reactivity of CS, a binding to nuclear proteins could be detected with specific activities ranging between 50 and 121 dpm/mg for liver and between 3 and 41 dpm/mg for kidney. Protein binding could well be responsible for its pronounced cytotoxic effects. CS was also tested in the Ames Salmonella/microsome assay. Strains TA 1535, TA 1537, TA 1538, TA 98, and TA 100 were used with or without pre-incubation. Only with strain TA 100 and only without pre-incubation, a doubling of the number of revertants was detectable at the highest dose levels used, 1,000 and 2,000 ug CS per plate. With pre-incubation of TA 100 with CS, a slight increase of the number of revertants was seen at 100 and 500 ug per plate, and a subsequent fall below control values at 1,000 ug. A check for the number of surviving bacteria revealed a strong bacteriotoxicity of the higher doses of CS so that the calculated mutation frequencies, ie, the number of revertants per number of surviving bacteria, increased with doses up to 500 ug. This toxicity could be counteracted in part by the addition of increasing amounts of rat liver microsomes. In the view of these results, and taking into account the rare and low exposure of man, it is concluded that CS will not create a risk for the induction of point mutations or of carcinogenic processes mediated by DNA binding. (Author abstract) (26 Refs)

ALTERATION OF MIXED FUNCTION OXIDASES BY CARCINOGENS

34. ACTIVATION OF BENZO(A)PYRENE AND 2-ACETAMIDOFLUORENE TO MUTAGENS BY MICROSOMAL PREPARATIONS FROM DIFFERENT ANIMAL SPECIES: ROLE OF CYTOCHROME P-450 AND P-448.

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Xenobiotica; 11(10):701-708 1981

The metabolic activation of benzo(a)pyrene and 2-acetamidofluorene to mutagens was studied with liver microsomal preparations from rat, guinea-pig, hamster and mouse, untreated or pretreated with phenobarbitone or 3-methylcholanthrene. Liver microsomal preparations from all animal species activated benzo(a)pyrene, that from mouse being the most efficient. Similarly, microsomal preparations from guinea-pig, hamster and mouse could activate 2-acetamidofluorene, but that from rat exhibited very weak activity. Activation of benzo(a)pyrene into mutagenic intermediates by liver microsomal preparations was increased for all animals except mouse by pretreatment with 3-methylcholanthrene. In contrast, pretreatment with phenobarbitone decreased the activation by microsomal preparations from all species. Activation of 2-acetamidofluorene by liver microsomal preparations from rat and guinea-pig, but not mouse and hamster, was increased by pretreatment of the animals with phenobarbitone. Pretreatment with 3-methylcholanthrene decreased the activation of this carcinogen by microsomal preparations from all species. The metabolic activation of benzo(a)pyrene is catalyzed by cytochrome P-448 but not cytochrome P-450. The activation of 2-acetamidofluorene to mutagens may involve, in addition to the mixed-function oxidases, other microsomal enzyme systems. (Author abstract) (29 Refs)

35. STRUCTURAL GENE PRODUCTS OF THE AH LOCUS. EVIDENCE FOR MANY UNIQUE P-450-MEDIATED MONOOXYGENASE ACTIVITIES RECONSTITUTED FROM 3-METHYLCHOLANTHRENE-TREATED C57BL/6N MOUSE LIVER MICROSOMES.

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Developmental Pharmacology Branch, Natl. Inst. Child Health and Human Development, NIH, Bethesda, MD, 20205

J Biol Chem; 256(23):12058-12067 1981

Cytochrome P-450 from cholate-solubilized liver microsomes prepared from 3-methylcholanthrene-treated genetically 'responsive' C57BL/6N mice (Ahb/Ahb) was partially purified by aminooctyl-Sepharose 4B column chromatography with an elution buffer that included Emulgen 911, followed by hydroxylapatite column chromatography. The P-450 was separated into 16 fractions: 15 fractions principally associated with the Ahb allele and induction by 3-methylcholanthrene and 1 fraction not associated with the Ahb allele, ie predominantly constitutive form(s) of P-450. The metabolism of benzo[a]pyrene, 7-ethoxycoumarin, biphenyl, ethoxyresorufin, acetanilide, 2-acetylaminofluorene, phenacetin, estradiol-17beta, and testosterone was investigated. With these nine substrates, we examined the rates of formation of 17 products, ie 17 P-450-mediated reconstituted monooxygenase 'activities,' in each of the 16 fractions. Differing reductase/cytochrome and lipid/cytochrome requirements were observed for each activity; the reasons for these empirical differences are not known. By two-factor analysis of variance, our data for 17 catalytic activities can be explained by a minimum of 19 unique groups of monooxygenase activities: 12 induced by 3-methylcholanthrene and 7 control (endogenous). At least one of these distinctly different 3-methylcholanthrene-induced groups and at least one of these constitutive groups is associated with a marked blue spectral shift (approx 2.0 nm) in the Soret peak of the reduced hemoprotein-CO complex, suggesting multiple forms of inducible and control 'P-448.' Almost every reconstituted monooxygenase activity therefore appears to be unique and probably represents the aggregate activity from numerous forms of P-450. (Author abstract) (43 Refs)

36. PRESENCE OF BENZO[A]PYRENE METABOLIZING ACTIVITIES IN ISOLATED RAT LIVER NUCLEOLI.

Lafarge-Frayssinet C, Alexandrov K, Rimbaut C, Dansette PM, Mousset S, Frayssinet C
Institut de Recherches Scientifiques sur le Cancer, BP No. 8, 94802 Villejuif Cedex, France
Carcinogenesis; 2(11):1189-1193 1981

A benzo[a]pyrene (B[a]P) hydroxylase activity and epoxide hydrolase (EH) activity have been found in rat liver nucleoli obtained from untreated (C) and 3-methylcholanthrene (3-MC) pretreated rats. A comparison of the enzyme activities was made in rat nuclei and nucleoli. Light and electron microscopic observations of nucleolar preparations did not reveal significant contamination either by intact nuclei or by nuclear membranes, and glucose 6-phosphatase, a marker of microsomal activity, was not detected in our nucleolar preparations. NADPH cytochrome c-reductase could be measured in C and 3-MC nuclei and very low but detectable activity was found in the nucleoli. Nucleolar preparations revealed significant hydroxylating activity, which was inducible by 3-MC in nuclei but not in nucleoli. The presence of EH in nucleoli was demonstrated with phenanthrene 9,10-oxide and B[a]P 4,5-oxide, but the nucleolar activities were lower than those obtained using intact nuclei. The addition of 1,1,1-trichloropropene 2,3-oxide completely inhibited EH activity. Furthermore the presence of covalently-bound metabolites of B[a]P formed in isolated nucleoli was demonstrated by cytofluoromicroscopy. (Author abstract) ([illegible]0 Refs)

37. GENETIC EVIDENCE FOR MANY UNIQUE LIVER MICROSOMAL P-450-MEDIATED MONOOXYGENASE ACTIVITIES IN HETEROGENEIC STOCK MICE.

Lang MA, Gielen JE, Nebert DW
Developmental Pharmacology Branch, Natl. Inst. Child Health and Human Development, NIH, Bethesda, MD, 20205
J Biol Chem; 256(23):12068-12075 1981

Total cytochrome P-450 content, the Soret maximum of the reduced P-450-CO complex, NADPH-cytochrome c reductase activity, and 20 monooxygenase activities were determined in liver microsomes from each of 12 individual Heterogeneic Stock (HS) mice at varying times after 3-methylcholanthrene treatment. The choice of genetically very heterogeneous mice and the possibility of different turnover rates (synthesis/degradation) during the 3-methylcholanthrene induction process provided us with a strong likelihood of detecting differences in drug-metabolizing enzyme activities. Such diversity would also be expected among the human population. The substrates included benzo[a]pyrene, ethoxyresorufin, biphenyl, p-nitroanisole, 2-acetylaminofluorene, 7-ethoxycoumarin, zoxazolamine, estradiol-17beta, testosterone, progesterone, pregnenolone, dehydroepiandrosterone, and aldrin. By two-factor analysis of variance, 18 unique liver microsomal monooxygenase activities appear to be distinctly different from one another, out of the 20 activities chosen for study. Ethoxyresorufin O-deethylase activity is significantly correlated ($p = 0.11$) with aryl hydrocarbon (benzo[a]pyrene) hydroxylase activity. Dehydroepiandrosterone 16alpha-hydroxylase activity correlates well with the testosterone ($p = 0.33$), progesterone ($p = 0.16$), and pregnenolone ($p = 0.11$) 16alpha-hydroxylases. Testosterone 16alpha-hydroxylase, progesterone 16alp ha-hydroxylase, and pregnenolone 16alpha-hydroxylase activities, on the other hand, are all significantly (p less than 0.001) different from one another. These data with intact microsomes illustrate the complexity of the problem with multiple P-450-mediated monooxygenases. Almost every activity therefore appears to be unique and probably reflects the aggregate contribution from numerous forms of P-450. (Author abstract) (33 Refs)

ALTERATION OF OTHER CARCINOGEN-METABOLIZING ENZYMES BY CARCINOGENS

38. SIALIC ACID METABOLISM IN NUTRITIONALLY MODULATED MAMMARY GLAND CARCINOGENESIS.

Fox OF, Kishore GS, Carubelli R
Biomembrane Res. Lab., Oklahoma Medical Res. Foundation, 825 Northeast Thirteenth St., Oklahoma City, OK, 73104
Cell Mol Biol; 27(5):473-482 1981

The activities of CMP-N-acetylneuraminic acid synthetase, sialyltransferase and neuraminidase were investigated in female Sprague-Dawley rats with mammary adenocarcinomas induced by oral administration of 7,12-dimethylbenz[a]anthracene. The carcinogenic process was modulated by the levels and degree of unsaturation of the dietary lipids in the presence and in the absence of dietary antioxidants. The activities of the biosynthetic enzymes responsible for the activation and transfer of sialic acids, ie CMP-N-acetylneuraminic acid synthetase and sialyltransferase were higher in tumors than in control mammary glands. The cytosolic and membrane-bound neuraminidases, on the other hand, were higher in control tissue than in tumors. In the low-fat dietary group, which had the lowest rate of tumor incidence, a tocopherol effect on sialic acid metabolism was detected; rats fed low-fat diet supplemented with alpha-tocopherol exhibited the highest levels of control mammary gland sialyltransferase activity, whereas tocopherol deficiency was accompanied by a loss of the tumor-dependent enhancement of CMP-N-acetylneuraminic acid synthetase. The enzyme profiles in the livers of control and tumor-bearing rats, although less well defined, showed some of the general trends observed in mammary tissues. (Author abstract) (21 Refs)

39. PHOSPHOLIPASE ACTIVITY IN SKIN AFTER APPLICATION OF PHORBOL ESTERS AND 3-METHYLCHOLANTHRENE.

Bresnick E, Bailey G, Bonney RJ, Wightman P
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Carcinogenesis; 2(11):1119-1122 1981

Topical administration of the promoter, 12-O-tetradecanoylphorbol-13-acetate (TPA), is accompanied by an increased incorporation of [3H]arachidonic acid into mouse skin and a very significant activation of epidermal cell membrane phospholipase A2 without affecting intracellular acid phospholipase. Similar enhancement in epidermal cell phospholipase A2 was observed after application of phorbol-12,13-didecanoate or 3-methyl-cholanthrene to mouse skin. A small but significant increase in phospholipase A2 activity is also seen after application of the nonpromoter irritant, acetic acid. The elevated levels of the prostaglandins observed in mouse skin after topical application of promoters are probably triggered by the activation of this membrane enzyme. (Author abstract) (25 Refs)

40. EXPRESSION OF THE TUMOR ALDEHYDE DEHYDROGENASE PHENOTYPE DURING 2-ACETYLAMINOFLUORENE-INDUCED RAT HEPATOCARCINOGENESIS.

Lindahl R, Evces S, Sheng WL
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Cancer Res; 42(2):577-582 1982

In aromatic amine-induced rat hepatomas, the aldehyde dehydrogenase (AlDH) phenotype is qualitatively and quantitatively different from that of normal liver. To identify the mechanism(s) underlying the expression of the tumor-specific AlDHs, we have followed the time course of appearance of the new phenotype during hepatoma formation in Sprague-Dawley rats following brief dietary exposures to 2-acetylaminofluorene (0.02%; 32 days). Tumor promotion by phenobarbital (0.05% in the diet) was also used to compare the effects of a variety of tumor induction protocols on the AlDH phenotype. No change in the AlDH phenotype is detectable by total activity assay, gel electrophoresis, isoelectric focusing, or immunochemical methods during or following exposure to carcinogen or promoter until tumors are grossly observed in liver. Concomitant with tumor appearance, the tumor-specific AlDH phenotype appears. The phenotypic change is limited to the tumor; morphologically and histologically normal liver directly adjacent to the tumor and normal lobes of a tumor-bearing liver do not possess the tumor AlDH phenotype. No correlation exists between tumor size and the degree of deviation of the AlDH phenotype from normal. Nor is there any correlation between the degree of AlDH phenotype deviation and the histology of the various tumors observed. We conclude that the tumor-specific AlDH phenotype is not associated with altered liver metabolism due directly to carcinogen or promoter exposure. Rather, the mechanism of this phenotypic change requires that transformation-associated, stable genetic changes occur in the cells affected by carcinogen that are later expressed as the altered AlDH phenotype. (Author abstract) (22 Refs)

41. EFFECT OF INDOLE ON N-NITROSODIMETHYLAMINE DEMETHYLASE IN RATS TREATED WITH CARBON TETRACHLORIDE.

Mostafa MH, Ruchirawat M, Weisburger EK
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Food Cosmet Toxicol; 19(6):717-721 1981

Carbon tetrachloride (CCl4) significantly decreased N-nitrosodimethylamine demethylase activity in Fisher rats in a dose-dependent fashion. After indole treatment, however, demethylase a ctivity was increased, reaching a maximum after 6-12 days of indole feeding. The inhibitory action of CCl4 could be modified by indole feeding. (28 Refs)

42. INHIBITION OF ENZYMATIC DNA METHYLATION BY N-METHYL-N'-NITRO-N-NITROSOGUANIDINE IN HUMAN RAJI LYMPHOBLAST-LIKE CELLS.

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Int J Biochem; 13(12):1225-1232 1981

A single treatment of the human Raji lymphoblast-like cell line with N-methyl-N'-nitro-N-nitrosoguanidine caused undermethylation of DNA which persisted in cell cycles following treatment. A possible relationship of such demethylation with aberrant phenotypic expression is discussed. (36 Refs)

43. ELEVATED LEVELS OF ORNITHINE DECARBOXYLASE AND POLYAMINES IN THE KIDNEYS OF ESTRADIOL-TREATED MALE HAMSTERS.

Nawata H, Yamamoto RS, Poirier LA
Nutrition and Metabolism Section, Lab. Carcinogen Metabolism, NCI, Bethesda, MD, 20205
Carcinogenesis; 2(11):1207-1211 1981

The effects of 17 beta-estradiol (E2) on the levels of ornithine decarboxylase (ODC), S-adenosylmethionine decarboxylase (SAMDC), and of the polyamines putrescine, spermidine and spermine in the kidneys of castrated male hamsters were determined. The ip injection of E2 into male hamsters led to renal ODC levels three times above the control levels 6-12 hr after treatment. Similarly, the renal ODC levels in hamsters treated with chronic doses of E2 for 60-180 days were 1.5-1.9 times the corresponding enzyme levels in control, sham-operated animals. With a series of estrogen analogues, there was a direct correlation between the rise in renal ODC in vivo and the binding to renal estradiol receptor sites in vitro. The hamster kidney levels of the polyamines putrescine, spermidine and spermine all declined during the 180-day experimental period. A single ip injection of E2 led to a 70% increase in renal SAMDC activity 12 hr after treatment. However, the administration of E2 for 180-270 days was without effect on the normal age-dependent decline in SAMDC levels noted in kidneys. These results indicate that, like other carcinogens and promoters, E2 increases the levels of ODC and of polyamines in its target tissue and that the rise in ODC is mediated by a specific estradiol-binding protein. (Author abstract) (30 Refs)

44. DIMINUTION OF MOUSE EPIDERMAL SUPEROXIDE DISMUTASE AND CATALASE ACTIVITIES BY TUMOR PROMOTERS.

Solanki V, Rana RS, Slaga TJ
Biology Div., Cancer and Toxicology Program, Oak Ridge Natl. Lab., Oak Ridge, TN, 37830
Carcinogenesis; 2(11):1141-1146 1981

The effects of phorbol ester tumor promoters and related compounds on superoxide dismutase (SOD) and catalase were examined. The treatment of adult mouse skin with 2 ug 12-O-tetradecanoylpho rbol-13-acetate (TPA) resulted in a sustained decrease in the basal levels of both SOD and catalase activities in the epidermis. A decline in SOD activity occurred within 3 hr after application and the maximum effect was seen at 16-17 hr. The decrease in SOD activity was always accompanied by a similar decline in the epidermal catalase activity. The alterations in both enzymes occurred against a high background of enhanced protein synthesis which indicates that the effect of TPA is selective for SOD and catalase. Other tumor promoters such as phorbol 12,13-dibutyrate and the non-phorbol tumor promoter anthraline also lowered the activities of both the enzymes. Mezerein, a resiniferonol derivative with weak promoting activity but a potent Stage-II promoter, appeared to be more potent than TPA in lowering the basal levels. These results indicate that damage which favors neoplastic progression could occur in TPA-treated mouse skin due to the accumulation of free radicals resulting from low levels of SOD and catalase activity. In addition, the TPA-caused decrease in the levels of SOD and catalase was not prevented by either retinoic acid, fluocinolone acetonide, tosyl amino-2-phenylethyl chloromethyl ketone, or butylated hydroxytoluene, suggesting that inhibition of tumor promotion by these agents is not mediated through alterations in the levels of enzymatic activities which decrease free radical concentrations. (Author abstract) (29 Refs)

45. DELAYED INDUCTION OF ORNITHINE DECARBOXYLASE IN MOUSE SKIN AFTER IRRADIATION WITH BETA-RAYS.

Fujiki H, Mori M, Tanooka H
National Cancer Res. Inst., Tsukiji 5-1-1, Chuo-ku, Tokyo 104, Japan
Cancer Lett; 15(1):15-17 1982

Delayed increase of ornithine decarboxylase (ODC) activity in mouse skin after irradiation with 90Sr-90Y beta rays was studied. Female 8-wk-old CD-1 mice were used in all experiments. The hair on their backs was clipped and further removed 2-3 days before irradiation. The shaved area was irradiated with beta-rays from the 90Sr-90Y source plated on 2-cm diameter metal disk for 13 min at a dose of 230 rad/min on the surface of the skin. Total irradiation dose was 3 kilorad. ODC activity for untreated mice was 0.01 nanomole CO_2/30 min/mg protein. The ODC activity remained at the control level until day 14 and then increased to max on about day 17; ODC activity decreased after that, reaching the starting level on about day 20. The visible acute skin reaction was also delayed, reaching max on day 16-20. Beta rays differ from tumor promoters and carcinogens in causing delayed ODC induction. Results indicate that beta rays induce a phenotypic change associated with tumor promotion. (7 Refs)

REVIEWS AND OTHER RELEVANT STUDIES

46. CURRENT CONCEPTS AND CONTROVERSIES IN CHEMICAL CARCINOGENESIS.

Weinstein IB
Div. Environmental Sciences, Inst. Cancer Res., Columbia Univ. Coll. Physicians and Surgeons, New York, NY, 10032
J Supramol Struct Cell Biochem; 17(2):99-120 1981

Fundamental research at the cellular and molecular levels on mechanisms of action of chemical carcinogenesis and applied aspects and the concept of 'molecular epidemiology' of cancer are reviewed. The action of initiating agents and their metabolism and covalent binding to macromolecules is discussed under the following headings: metabolic activation, carcinogen potency, structures of carcinogen-DNA adducts, conformational changes in DNA, carcinogen modification of mitochondrial DNA, DNA repair, and carcinogen-DNA modification and mechanism of initiation. Tumor promotion and multifactor interactions are discussed in relation to two-stage skin carcinogenesis. Numerous effects elicited by phorbol ester tumor promotors, particularly 12-O-tetradecanoyl-phorbol-13-acetate, are classified into three categories: mimicry of transformation, modulation of differentiation, and membrane effects. Also considered in relation to phorbol ester tumor promotors, tumor promotion, and multifactor interactions are phorboid receptors, ion flux, possible role of kinases, chromosomal effects and activated oxygen, and chemical-viral interactions. The tumor-promoting activity of polycyclic aromatic hydrocarbons is discussed. A unified theory of tumor initiation and promotion is presented. Molecular epidemiology and cancer prevention are discussed with regard to limitations of current approaches and molecular cancer epidemiology. (94 Refs)

47. TYPES OF MATERIALS AND TESTS (MEETING ABSTRACT).

Bridges JW, Hubbard SA
Robens Institute of Industrial and Environmental Health and Safety, University of Surrey Guildford, GU2 5XH, England
Mutagenicity Testing, October 12, 1981, London, England, Royal Society of Chemistry; 1981

Many carcinogens exert their effects indirectly through the formation of reactive metabolites. The formation of these reactive metabolites is brought about by the drug metabolizing enzymes of the cell, a group of enzymes whose primary role appears to be the conversion of lipid soluble substances to water soluble excretable products. In many mutagenicity tests a 9,000 xg fraction of rat liver homogenate (S9) is added to mimic the in vivo ability of tissues to form these reactive metabolites. The quantity and quality of S9 fraction which is added may cause large variations in the observed mutagenic response. The degree of mutagenicity is also affected greatly by the previous chemical exposure and diet of the rats from which the S9 fraction is derived. A number of other factors are also very important: a) The form in which the chemical is presented to the biological system. Particular problems are often experienced in assessing the mutagenicity of insoluble particulates, intensely colored materials, volatile su bstances and compounds which bind avidly to plastic. b) The medium in which the metabolizing and mutagenic response systems are suspended and the nature of any cellular membranes between them. This influences the passage of any reactive metabolites formed into the response system. c) The nature of the response system itself. No single set of experimental conditions is ideal for assessing the mutagenicity of all chemicals, rather the experimental conditions should be selected bearing in mind the physical and chemical properties of the material which is being tested. (no Refs)

48. TOXIC DRUG EFFECTS ASSOCIATED WITH OXYGEN METABOLISM: REDOX CYCLING AND LIPID PEROXIDATION.

Kappus H, Sies H
Inst. Umwelthygiene, Univ. Dusseldorf, Moorenstrasse 5, D-4000 Dusseldorf, W. Germany
Experientia; 37(12):1233-1241 1981

Various endogenous and exogenous compounds exert cytotoxic effects via oxygen reduction. In general, these are reduced by intracellular enzymes (reductases of various kinds) in one-electron transfer reactions, before they in turn reduce O_2 to O_2^-, the superoxide anion radical. Thus, a cycle is formed of O_2 uptake at the expense of cellular reducing equivalents, notably NADPH, generating further active oxygen species. Structures capable of 'redox cycling' include catechols and other quinone compounds, iron chelates, and aromatic nitro compounds. Several anticancer agents, and also some mutagens, operate on this principle, and their toxic effects may be explained by redox cycling. The particular importance of hypoxic conditions for deleterious O_2 effects is given by the concomitant flux through reductive as well as oxidative pathways. Toxic effects include membrane damage resulting from peroxidative reactions of polyunsaturated fatty acids (lipid peroxidation), as well as the attack of reactive oxygen species on proteins (enzymes) and nucleic acids; thus O2 metabolism is linked to carcinogenicity and mutagenicity. Lipid peroxidation is also induced by various halogenated compounds such as carbon tetrachloride. Again, hypoxic conditions are particularly critical because, on the one hand, metabolic activation leading to the free radical is enhanced and, on the other hand, oxygen required for the maintenance of lipid peroxidation is still available. Powerful antioxidant systems of the cell maintain low steady state concentrations of oxygen metabolites, and toxic effects may, in part, also be explained by the constant drain of reducing equivalents resulting from redox cycling. (Author abstract) (137 Refs)

49. EFFECTS OF STRUCTURE ON THE CARCINOGENIC BEHAVIOR OF NITROSAMINES.

Wishnok JS
Dept. Nutrition and Food Sciences, Massachusetts Inst. Technology, Cambridge, MA, 02139
ACS Symp Ser; 174():77-87 1981

Small, closely-related series of nitrosamines have been examined and a quantitat ive structure-activity model (QSM) based on molecular descriptors (physicochemical, geometrical, topological, and electronic) has been developed. The final form of QSM can be interpreted in terms of the proposed mechanisms of action or of modified aspects of these mechanisms. Nitrosamines are highly sensitive towards one or a few target organs. Test compounds included 13 dialkylnitrosamines which induced tumors in the liver or in the lung or esophagus. All test compounds were administered at equal daily doses. Relative properties of compounds reflect then only the differences in the molecular structure of the test substances. The model for organ selectivity requires terms for the parent nitrosamine as well as for the hypothesized metabolites while the model for potency variations contains terms only for the unmetabolized parent compound. (29 Refs)

50. HISTOLOGICAL EVIDENCE OF 'ESTROGENIC PROPERTIES' OF 7,12-DIMETHYLBENZ(A)ANTHRACENE.

Valero D, Drouhault R, Vanhems E, Bousquet J, Blanquet P

Unite 53, I.N.S.E.R.M., Domaine de Carreire, Rue Camille Saint-Saens, 33077 Bordeaux Cedex, France

Cell Mol Biol; 27(2/3):263-269 1981

DMBA (7,12-dimethylbenz(a)anthracene) and estradiol provoke in rat pituitaries an increase of prolactin cells number and of hormone synthesis. It is a transitory effect. Both enhance equally G6PD activity, this enzyme acting for an end product of a functional estradiol receptor. This increased reactivity persists during mammary tumor growth. These data added to previously published results, support the hypothesis that carcinogen would act in part by 'estrogen-mimetic' properties. (Author abstract) (25 Refs) (In FRE)

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CHEMICAL CARCINOGENESIS

1. ETHYLENE OXIDE (ETO): EVIDENCE OF CARCINOGENICITY.
Coene RF
National Inst. for Occupational Safety and Health, Cincinnati, OH
Vet Hum Toxicol; 23(6):439-443 1981

DIETARY FACTORS IN CARCINOGENESIS

2. NUTRITIONAL ASPECTS OF CANCER PREVENTION: AN OVERVIEW.
Silverman J
American Health Foundation, Naylor Dana Inst Disease Prevention, Valhalla, NY, 10595
J Am Vet Med Assoc; 179(12):1404-1409 1981

3. FORMATION OF N-NITROSO COMPOUNDS IN FOODS.
Gray JI
Dept. Food Science and Human Nutrition, Michigan State Univ., East Lansing, MI, 48824
ACS Symp Ser; 174():165-180 1981

EPIDEMIOLOGY, ETIOLOGY AND GENETIC ASPECTS OF HUMAN CANCER

4. LYMPHOMAS AND LEUKAEMIAS. PART 2: TROPICAL AMERICA.
Jimenez E
Hospital Nacional de Ninos 'Dr. Carlos Saenz Herrera', Apartado 1654, San Jose, Costa Rica
Clin Haematol; 10(3):894-915 1981

5. LYMPHOMAS AND LEUKAEMIAS. PART 1: TROPICAL AFRICA.
Olweny CL
Uganda Cancer Inst., P.O. Box 3935, Kampala, Uganda
Clin Haematol; 10(3):873-893 1981

6. MALIGNANT MELANOMA.
Creagan ET
Div. Medical Oncology, Mayo Clinic, Rochester, MN, 55905
Compr Ther; 7(12):36-44 1981

7. MELANOTIC TUMORS OF THE UVEA AND RETINA.
Schmitt H
Universitats-Augenklinik, Theodor-Stern-Kai 7, D-6000 Frankfurt am Main, W. Germany
Med Klin; 76(24):672-675 1981
In GER

CELLULAR AND MOLECULAR MECHANISMS IN CARCINOGENESIS

8. THE NATURAL HISTORY OF CARCINOGENESIS: IMPLICATIONS OF EXPERIMENTAL CARCINOGENESIS IN THE GENESIS OF HUMAN CANCER.
Pitot HC, Goldsworthy T, Moran S
McArdle Lab. for Cancer Res., Dept. Oncology, Medical Sch., Univ. Wisconsin, Madison, WI, 53706
J Supramol Struct Cell Biochem; 17(2):133-146 1981

9. CURRENT CONCEPTS AND CONTROVERSIES IN CHEMICAL CARCINOGENESIS.
Weinstein IB
Div. Environmental Sciences, Inst. Cancer Res., Columbia Univ. Coll. Physicians and Surgeons, New York, NY, 10032
J Supramol Struct Cell Biochem; 17(2):99-120 1981

VIRAL AND IMMUNOLOGICAL ASPECTS OF CARCINOGENESIS

10. BURKITT'S LYMPHOMA.
Ambrus JL, Ambrus CM
Roswell Park Memorial Inst., 666 Elm St., Buffalo, NY, 14263
J Med; 12(6):385-413 1981

11. PRIMARY HEPATIC CARCINOMA.
Iosquin CJ
Catedra de Medicina Interna A, Facultad de Ciencas Medicas, La Plata, Argentina
Rev Fac Cienc Med La Plata; 4(2):27-31 1981
In SPA

METHODOLOGY IN CARCINOGENESIS RESEARCH

12. MUTAGENESIS AND CARCINOGENESIS TESTING IN VITRO.
Casto BC
Northrop Services, Incorporated, P.O. Box 12313, Research Triangle Park, NC, 277 09
Biotechnol Bioeng; 23(12):2659-2671 1981

OTHER REVIEWS IN CARCINOGENESIS

13. CANCER IN THE YEAR 2000. A REVIEW.
Saxen E
Suomen Syoparekisteri, Liisankatu 21 B, 00170 Helsinki 17, Finland
Duodecim; 97(20):1708-1716 1981
In FIN

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Activation and Metabolism of Carcinogens

SERIES CK08 No. 82/06

JUNE, 1982

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METABOLIC ACTIVATION OF CARCINOGENS

1. STEREOSELECTIVE METABOLISM OF THE OPTICAL ISOMERS OF TRANS-1,2-DIHYDROXY-1,2-DIHYDROPHENANTHRENE TO BAY-REGION DIOL EPOXIDES BY RAT LIVER MICROSOMES.

Vyas KP, Thakker DR, Levin W, Yagi H, Conney AH, Jerina DM
Lab. Bioorganic Chemistry, Natl. Inst. Arthritis, Metabolism and Diseases, NIH, Bethesda, MD, 20205
Chem Biol Interact; 38(2):203-213 1982

Enantiomerically pure isomers of trans-1,2-dihydroxy-1,2-dihydrophenanthrene have been obtained by chromatographic separation of their diastereomeric bis esters with (-)-alpha-methoxy-alpha-trifluoromethylphenylacetic acid. Liver microsomes from control rats, as well as rats treated with phenobarbital or 3-methylcholanthrene, metabolize these dihydrodiols to a pair of diastereomercially related bay-region 1,2-diol-3,4-epoxides in which the benzylic hydroxyl group and the epoxide oxygen are either cis (isomer-1) or trans (isomer-2) to each other. In general, diol epoxide-1 was the major metabolite of the (+)-(1S,2S)-dihydrodiol, whereas diol epoxide-2 was the major metabolite of the (-)-(1R-2R)-dihydrodiol. The extent of this stereoselectivity is dependent on the source of the microsomes and is greatest for liver microsomes from 3-methylcholanthrene-treated rats; the ratio of diol epoxide-1 relative to diol epoxide-2 was 5.6 : 1 with the (+)-enantiomer as substrate and 1 : 5.5 with the (-)-enantiomer as substrate. For a given microsomal preparation, rates of metabolism were independent of the enantiomer composition of the substrate. Relative to microsomes from control animals, treatment of rats with 3-methyl-cholanthrene enhanced rates of metabolism by about 40%, whereas treatment with phenobarbital decreased rates to a similar extent when the amounts of metabolites formed per nanomole of cytochrome P-450 were compared. The failure of treatment by 3-methylcholanthrene to enhance markedly the rate of metabolism of a polycyclic aromatic hydrocarbon substrate is unusual. (Author abstract) (16 Refs)

2. FUNGAL OXIDATION OF 3-METHYLCHOLANTHRENE: FORMATION OF PROXIMATE CARCINOGENIC METABOLITES OF 3-METHYLCHOLANTHRENE.

Cerniglia CE, Dodge RH, Gibson DT
Natl. Center Toxicological Res., Food and Drug Admin., Jefferson, AK, 72079
Chem Biol Interact; 38(2):161-173 1982

The filamentous fungus, Cunninghamella elegans, was found to metabolize the potent carcinogen, 3-methylcholanthrene (3-MC) to 1-hydroxy-3-MC, 2-hydroxy-3-MC, 1-keto-3-MC, 2-keto-3-MC and trans-9,10-dihydrodiols of 1-hydroxy-3-MC. In addition several unidentified derivates of 3-MC were found. The metabolites formed were separated by high pressure liquid chromatography (HPLC) and identified by comparison of retention times, absorbance, fluorescence and mass spectra with those of synthetic standards. Incubation of (+-)-1-hydroxy-3-MC and (+-)-2-hydroxy-3-MC with cells of C elegans indicated that 1-hydroxy-3-MC is metabolized to form diastereomerically related trans-9,10-dihydrodiols of 1-hydroxy-3-MC. Experiments with 3-[14C]MC showed that over a 48-hr period, 8.7% of the hydrocarbon was oxidized to organic solvent-soluble metabolic products. Most of the metabolites were polar products, some of which co-chromatographed with trans-9,10-dihydrodiols of 1-hydroxy-3-MC. The results show that C elegans has the ability to oxidize 3-MC to metabolites that have been implicated as proximate carcinogenic forms of 3-MC in higher organisms. (Author abstract) (34 Refs)

3. THIN-LAYER CHROMATOGRAPHIC AND HIGH-PERFORMANCE LIQUID CHROMATOGRAPHIC SEPARATION OF METABOLITES OF THE WEAK CARCINOGEN, 7-METHYLBENZ[C]ACRIDINE.

Boux LJ, Ireland CM, Wright DJ, Holder GM, Ryan AJ
Dept. Pharmacy, Univ. Sydney, Sydney, N.S.W. 2006, Australia
J Chromatogr; 227(1):149-157 1982

The metabolism of [14C]7-methylbenz[c]acridine, a weakly carcinogenic polycyclic aza aromatic hydrocarbon, was studied in rats in vivo, and in rat hepatocytes and hepatic microsomes. Evidence for oxidation of the methyl group and excretion of 7-hydroxymethyl-benz[c]acridine and benz[c]acridine-7-carboxylic acid in rat bile was bile was obtained by thin-layer chromatography. A reversed-phase high-performance liquid chromatographic separation of metabolites was developed and chromatographic profiles of metabolites found in vivo and formed in vitro are presented. Several synthetic potential oxidation products were used to characterize the chromatographic profiles and evidence for the in vitro formation of 7-hydroxymethylbenz[c]acridine and 5,6-dihydro-5,6-dihydroxy-7-methylbenz[c]acridine was obtained. (Author abstract) (35 Refs)

4. METABOLISM OF 2-ACETYLAMINOFLUORENE IN PRIMARY RAT HEPATOCYTE CULTURES.

Spilman SD, Byard JL
(c/o Byard) Dept. Environmental Toxicology, Univ. California, Davis, CA, 95616
J Toxicol Environ Health; 7(1):93-106 1981

The kinetics of 2-acetylaminofluorene (AAF) metabolism are investigated at various doses and with varying cell culture conditions. Primary cultures of 2 x 10(6) Sprague-Dawley rat hepatocytes metabolized all of a dose of 137 ng of 13.7 ug AAF during 12-24 hr of incubation. At higher concentrations of AAF per 2 x 1(6) cells, the rate of metabolism diminished and water-soluble metabolites appeared at 70% the rate at lower doses. Presumptive covalently bound AAF residues reached a max of 5% of the adminstered 137 ng per 2 x 10(6) M cells. The rate of appearance of water-soluble AAF metabolites was stimulated by the addition of hormones to the culture medium, correlating with the enhanced cytochrome P-450 levels in hormone-treated cells. With 10(-4) M SKF 525A, the metabolism of AAF was diminished 50%; with 10(-3) M, it was eliminated. With 40 ug AAF per 2 x 10(6) cells, 31% of AAF was recovered as water-soluble products after 24 hr. The cells could then metabolize a subsequent 40-ug dose at an undiminished rate. Thus, primary rat hepatocyte cultures constitute an in vitro model for the quantitative study of the cellular disposition of a chemical careinogen in its presumptive target cell. (43 Refs)

5. METABOLISM OF DICHLOROBIPHENYLS BY HIGHLY PURIFIED ISOZYMES OF RAT LIVER CYTOCHROME P-450.

Kaminsky LS, Kennedy MW, Adams SM, Guengerich FP
Div. Lab. and Res., New York State Dept. Health, Albany, NY, 12201
Biochemistry; 20(26):7379-7384 1981

Hepatic mixed-function oxidase metabolism of the ubiquitous pollutant polychlorinated biphenyls (PCBs) is implicated in their toxification and detoxification. We used dichlorobiphenyls (DCBs) as models to investigate the effect of the chloro substituent sites on this metabolism experimentally and by molecular orbital calculations. Reconstituted, purified cytochrome P-450 PB-B and BNF-B, the major terminal oxidase isozymes of this system, from phenobarbital (PB)- and beta-naphthoflavone (BNF)-induced rats were used to investigate this metabolism. Both isozymes are also induced by PCBs. High-performance liquid chromatography (HPLC) was used to detect, quantify, and isolate metabolites. Metabolite structures were identified by mass spectrometry, dechlorination to identifiable hydroxybiphenyls, and HPLC retention times. All DCBs yielded 3-and 4- but no 2-monohydroxylated metabolites (3,3'-DCB also yielded a dihydroxy metabolite). Di-o-chloro-substituted DCBs were metabolized primarily by cytochrome P-450 PB-B, mono-o-chloro substituted DCBs by both isozymes approx equivalently, and DCBs without o-chloro substituents by BNF-B primarily. Thus PB-B preferentially metabolizes noncoplanar DCBs and BNF-B coplanar DCBs. The cytochrome isozymes exhibited differing regioselectivities for DCB metabolism-PB-B hydroxylated unchlorinated phenyl rings and BNF-B chlorinated rings. Incorporation of epoxide hydrolase yielded DCB dihydrodiols, and hydroxy metabolite patterns were consistent with those calculated from ring-opened arene oxide intermediates. Thus the rates and regioselectivities of metabolism and thus possibly the toxicity and carcinogenicity of DCBs are dependent on the cytochrome P-450 isozymes induced. (Author abstract) (42 Refs)

6. REACTIVE METABOLITES AND CARCINOGENICITY OF HALOGENATED ETHYLENES.

Bolt HM, Laib RJ, Filser JG
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Biochem Pharmacol; 31(1):1-4 1982

Mutagenicity and carcinogenicity of halogenated ethylenes (HE) are reviewed with special emphasis on the role of molecular rearrangement in metabolic detoxication. Comparison of the data on the formation of hepatic preneoplastic foci after exposure of young Wistar rats to HE with the metabolic data showed significant reduction of the wide range of oncogenic activities when the preneoplastic effects were related to the amount of HE metabolites produced after 400 hr of exposure. It is suggested that monochlorooxirane (the epoxide of vinyl chloride) represents an optimum between stability and reactivity to reach the DNA target and react with it. (47 Refs)

OTHER METABOLISM OF CARCINOGENS

7. KINETICS OF GLUCURONIDATION OF PHENOL-DERIVATIVES OF BENZO(A)PYRENE WITH RAT AND MOUSE LIVER MICROSOMES.

Nemoto N, Takayama S
Dept. Experimental Pathology, Cancer Inst., Kami-Ikebukuro, Toshima-ku, Tokyo 170, Japan
Toxicol Lett; 10(1):75-79 1982

Male Wistar rats (100-125 g) and male C57BL/6 and DBA/2 mice (6 wk old) were injected ip with 3-methylcholanthrene (3-MC, 100 mg/kg), and liver microsomal uridine diphosphate-glucuronyl transferase was assayed by the method of Nemoto and Gelboin. Studies of the kinetics of glucuronidation with 3-hydroxybenzo(a)pyrene and 9-hydroxybenzo(a)pyrene reveal two apparent Km values for both compounds in both species. Km values were somewhat higher in liver microsomes of 3-MC-treated rats and mice than in the controls; the detergent Brij 58 (0.0125 %) also increased activities. The critical concentration of substrate was 2.5 uM for rats and 6.25 uM for mice. The transferase reaction is evidently either inhibited by concentrations above these amounts or activated by concentrations below them. (11 Refs)

MODIFICATION OF CARCINOGEN METABOLISM

8. EFFECTS OF 3-METHYLCHOLANTHRENE, BETA-NAPHTHOFLAVONE, AND PHENOBARBITAL ON THE 3-METHYLCHOLANTHRENE-INDUCIBLE ISOZYME OF CYTOCHROME P-450 WITHIN CENTRILOBULAR, MIDZONAL, AND PERIPORTAL HEPATOCYTES.

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Dept. Pharmacology, Toxicology Center, Coll. Medicine, Univ. Iowa, Iowa City, IA, 52242
J Biol Chem; 257(2):953-957 1982

Rabbit antiserum produced against cytochrome P-450 MC-B, the major isozyme of cytochrome P-450 isolated from hepatic microsomes of 3-methylcholanthrene-pretreated rats, was utilized in unlabeled antibody peroxidase-antiperoxidase and indirect fluorescent antibody staining techniques to investigate the effects of 3-methylcholanthrene, beta-naphthoflavone, and phenobarbital on the hemeprotein within centrilobular, midzonal, and periportal hepatocytes in livers of male rats. In livers of untreated and vehicle-pretreated rats, midzonal and periportal hepatocytes were found to bind the anti-cytochrome P-450 MC-B to equal extents while centrilobular hepatocytes bound approximately 25% more antibody. Pretreatment of rats with phenobarbital did not result in alterations in either the intensity or pattern of immunohistochemical staining for cytochrome P-450 MC-B within the liver lobule. In livers of rats which had been pretreated with 3-methylcholanthrene, microfluorometric analyses revealed that the extent of anti-cytochrome P-450 MC-B binding increased by approximately 215% within both the midzonal and periportal regions of the lobule and by approximately 150% within centrilobular regions. Pretreatment of rats with beta-naphthoflavone resulted in alterations in the hemeprotein which were similar to those produced by 3-methylcholanthrene. Thus, after rats had been pretreated with either 3-methylcholanthrene or beta-naphthoflavone, the pattern of intralobular distribution of cytochrome P-450 MC-B was altered so that the antibody bound to approximately equal extents to hepatocytes within the three regions of the lobule. These results demonstrate that 3-methylcholanthrene and beta-naphthoflavone exert similar inductive effects on cytochrome P-450 MC-B within the liver lobule, with the least degree of induction of the hemeprotein being produced within centrilobular hepatocytes. (Author abstract) (42 Refs)

9. ENZYMATIC CONTROL OF REACTIVE METABOLITES DERIVED FROM AROMATIC FOREIGN COMPOUNDS.

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Chimia; 35(10):405-406 1981

The relative importance of individual enzymes in biological activation of carcinogenic metabolites of aromatic compounds was studied using Salmonella typhimurium mutants and suspensions of liver microsomes. In control and phenobarbital-induced microsomes epoxide hydroxylase (EH) efficiently inactivated the metabolites. In 3-methylcholanthrene-induced microsomes EH had one weak multiphasic inactivating effect. (16 Refs)

10. PHORBOL-12,13-DIESTER 12-ESTER HYDROLASE MAY PREVENT TUMOUR PROMOTION BY PHORBOL DIESTERS IN SKIN.

Shoyab M, Warren TC, Todaro GJ
Lab. Viral Carcinogenesis, NCI, NIH, Frederick, MD, 21701
Nature; 295(5845):152-154 1982

The relationship between skin phorbol-12,13-diester 12-ester hydrolase (PDEH) level and species susceptibility to 12-O-tetradecanoylphorbol-13-acetate (TPA)-induced skin tumor promotion was studied. Enzyme activity was determined by incubating tissue extracts with 3H-phorbol-12,13-dibutyrate (3H-PDBu) for 30 min and measuring the amount of remaining 3H-PBDu by its binding to mouse brain membrane fractions (phorbol ester receptors). PDEH activity was absent in mouse skin but present at high levels in hamster, rat, guinea pig, and rabbit skin. Skin from all species contained TPA receptors, indicating that lack of responsiveness to TPA is not due to absence of specific TPA receptors. Extracts from hamster, rat, guinea pig and rabbit skin reduced 3H-PDBu receptor binding and converted the compound to biologically inactive phorbol-13-butyrate. Extracts from mouse, cat, dog, monkey, or human skin did not affect the binding or metabolism of 3H-PBDu. The results demonstrate that PDEH can inhibit tumor promotion by inactivating TPA and other active phorbol esters; active phorbol esters may act as tumor promotors in cat, dog, monkey, and human skin. (27 Refs)

MUTAGENICITY OF ACTIVATED METABOLITES OF CARCINOGENS

11. SYNERGISTIC EFFECTS OF INDIVIDUAL POLYCYCLIC AROMATIC HYDROCARBONS ON THE MUTAGENICITY OF THEIR MIXTURES.

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Mutat Res; 90(4):399-409 1981

Enhancement and inhibition of mutagenic activity (MA) of benzo[a]pyrene (B[a]P) by polycyclic aromatic hydrocarbons (PAH) was studied in Salmonella typhimurium strain TA98. S9 mix prepared from livers of Sprague-Dawley rats treated with Aroclor was used for metabolic activation. In the Ames assay bacterial cultures were exposed to B[a]P (0.5-3.0 ug/plate) with or without various PAH (less than or equal to 2,000 nanomoles/plate). Results obtained with PAH of 2-5 rings showed that all PAH tested enhanced MA of B[a]P. Naphthacene and benzo[e]pyrene enhanced MA of B[a]P at low concentrations but inhibited MA at higher concentrations. Neither naphthalene nor anthracene inhibited MA of B[a]P. Results indicate that the amount of PAH required for enhancement and inhibition effects decreases with increasing number of rings in the PAH structure. Several compounds with four rings, such as chrysene, pyrene, fluoranthene, and triphenylene, were exceptions to this rule. The effects of compounds with five or more rings were difficult to interpret because their own mutagenicity interfered with the synergistic effect on B[a]P mutagenicity, and inhibitory effects were evident in every case. Synergistic effects are apparently dependent on the spatial geometry rather than on specific properties of the PAH. PAH did not increase MA of benzo[a]pyrene-4,5-oxide, a direct-acting metabolite of B[a]P. Since B[a]P requires metabolic activation for MA, the result suggests that PAH exert synergistic effects at the level of enzymatic activation of B[a]P. (19 Refs)

12. A 7-HYDROXYMETHYL SULFATE ESTER AS AN ACTIVE METABOLITE OF 7,12-DIMETHYLBENZ[A]ANTHRACENE.

Watabe T, Ishizuka T, Isobe M, Ozawa N
Lab. Drug Metabolism and Toxicology, Dept. Hygienic Chemistry, Tokyo Coll. of Pharmacy, Horinouchi, Hachioji-shi, Tokyo 192-03, Japan
Science; 215(4531):403-405 1982

The compound 7-Hydroxymethyl-12-methylbenz[a]anthracene (7-HMBA), a carcinogenic major metabolite of 7,12-dimethylbenz[a]anthracene (DMBA) in liver, was transformed by liver cytosolic sulfotransferase to reactive 7-HMBA sulfate, which is mutagenic toward Salmonella typhimurium strain TA98. The mutagenicity of 7-HMBA in the presence of hepatic sulfotransferase was much higher than that of DMBA or 7-HMBA in the presence of hepatic monooxygenase. (Author abstract) (23 Refs)

13. SISTER CHROMATID EXCHANGE (SCE) INDUCTION BY PROMUTAGENS IN CULTURED HUMAN HEPATOMA CELLS (MEETING ABSTRACT).

Abe S, Sasaki M, Nemoto N
Chromosome Research Unit Fac Sci, Hokkaido University, Sapporo, Japan
Proceedings of the Japanese Cancer Association 40th Annual Meeting, October 1981, Sapporo, Japan. The Association 415 pp., 1981.

Cultured human hepatoma Hc-1 and Hc-4 cells were shown to produce an increased frequency of SCEs after treatment with benzo(a)pyrene (BP). Analysis of metabolism of BP by high pressure liquid chromatography indicated that Hc-1 and Hc-4 cells produce various kinds of BP metabolites including 7,8-dihydrodiol, a precursor of the ultimate metabolite of BP, which is supposedly responsible for induction of SCEs. Several other kinds of aromatic hydrocarbons, aflatoxin B1 and cyclophosphamide also induced SCEs in Hc-1 and Hc-4 cells. The findings suggest that Hc-1 and Hc-4 cells could convert a wide range of promutagens into active metabolites to induce SCEs, and may serve as simple in vitro screening systems for promutagens without exogenous activation systems. (no Refs)

14. METABOLIC ACTIVATION OF CARCINOGENS IN THE SALMONELLA MUTAGENICITY ASSAY BY HAMSTER AND RAT LIVER S-9 PREPARATIONS.

Raineri R, Polley JA, Pienta RJ, Andrews AW
Chemical Carcinogenesis Program, Fredrick Cancer Res. Center, Frederick, MD, 21701
Environ Mutagen; 3(1):71-84 1981

In the Salmonella mutagenicity assay, mutagenicity of the known carcinogens 2-acetylaminofluorene (AAF), 2-aminoanthracene (AA), 3-methylcholanthrene (MCA), benzo(a)pyrene (BP), and diethylnitrosamine (DEN) were directly compared using either uninduced or phenobarbital (PB)- or Aroclor (AC)-induced liver S-9 preparations from both male and female hamsters and rats. Effects of different concentrations of the S-9 protein were studied. Mutagenicity data were compared with the aryl hydrocarbon hydroxylase (AHH) and BP-4,5-epoxide hydrase (EH) activities of the liver S-9 preparations, and the levels of binding of BP metabolites to DNA were measured. The preparations from hamster liver were consistently more effective than those from rat liver for the activation of AAF, AA (except for AC-induced preparations), MCA, and DEN to their mutagenic forms. Induced preparations from rats were more active than those from hamsters when using BP. With the aromatic amines (AAF and AA), a partial inhibition of mutagenicity occurred at the highest protein concentrations tested. Inverse relationship was observed with BP between protein concentration and number of revertants occurring in the presence of the preparation from PB- and AC-induced male and female rats. Relative order of activities of AHH and EH in preparations was AC-induced greater than PB-induced greater than uninduced. An exception was the liver S-9 preparation from AC-induced female rat which induced no EH activity. Levels of binding of the metabolites of tritiated BP to calf thymus DNA were correlated with AHH levels except in the case of the preparation from PB-induced female rats, in which no binding was detected. (31 Refs)

15. MUTAGENICITY OF STYRENE IN THE SALMONELLA TYPHIMURIUM TEST SYSTEM.

de Meester C, Duverger-van Bogaert M, Lambotte-Vandepaer M, Mercier M, Poncelet F
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Mutat Res; 90(4):443-450 1981

Seven strains of Salmonella typhimurium were exposed to gaseous styrene. Styrene produced mutagenic effects in strains TA1530, TA1535, and TA100; mutagenesis required the presence of S9 from rats treated with Aroclor. A dose-effect relationship was established in TA1530. Mutagenic activity of styrene was weak. Results indicate formation of a volatile, unidentified intermediate compound by S9 enzymes. (22 Refs)

16. A CORRELATION BETWEEN MUTAGENIC AND CARCINOGENIC POTENCIES IN A DIVERSE GROUP OF N-NITROSAMINES: DETERMINATION OF MUTAGENIC ACTIVITIES OF WEAKLY MUTAGENIC N-NITROSAMINES.

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Carcinogenesis; 2(12):1339-1344 1981

The mutagenic activities of a diverse group of N-nitrosamines were measured in Salmonella typhimurium TA 100 under conditions designed to maximize metabolism of N-nitrosamines and enhance their mutagenic effects. These conditions were also chosen since some of the carcinogens were previously reported to be non-mutagenic or of questionable mutagenic activity and some only became mutagenic after the bacteria were exposed to a 'threshold dose' of metabolites. The mutagenic potencies spanned a range of 10(5)-fold and correlated well with semiquantitative carcinogenic potencies taken from the literature. This correlation appears to be the strongest yet reported for any particular class of compounds. In addition, the mutagenic activities of a number of carcinogens, previously reported to be non-mutagenic, were determined. Among the structural features necessary for high mutagenic activity in this group of compounds was a potential, unsubstituted methylating or ethylating group. Substitution of alkyl, hydroxyl methoxyl, and cyano moieties at the alpha or beta carbon of these groups reduced mutagenic activity. (Author abstract) (34 Refs)

17. INDUCTION OF SISTER CHROMATID EXCHANGES IN HUMAN DIPLOID FIBROBLASTS BY MUTAGENS WITH AND WITHOUT RAT LIVER MICROSOMAL ACTIVATION.

Yang DP, Graupensperger F, Minecci LC, Rubin BA
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Environ Mutagen; 3(1):45-52 1981

Effects of a promutagen, a plant clastogen, and two direct mutagens were tested on sister chromatid exchange (SCE) induction in WI-38 cells with and without rat liver microsomal activation. Exponentially growing cells, 24 hr after subcultivation were treated with cyclophosphamide (CY), maleic hydrazide (MH), N-methyl-N'-nitro-N-nitrosoguanidine (MNNG), and 4-nitro-quinoline-1-oxide (4NQO) at various concentrations in the growth medium at 37 C for 1 hr. The frequency of SCE was estimated by the 5-bromodeoxyuridine-dye technique with and without addition of rat liver microsomal suspension (S-9). CY concentrations from 1 x 10(-5) M to 1 x 10(-3) M with S-9 mix increased the number of SCE/cell in a dose-dependent manner. Without S-9 mix, CY concentrations less than 1 x 10(-3) M did not produce more SCE than the controls. MNNG at 1 x 10(-8) M and 4NQO at 1 x 10(-7) M without S-9 produced significant increases in SCE/cell. Addition of S-9 slightly decreased the effects of MNNG and 4NQO in the formation of SCE. MH was tested at pH 6.4 and pH 7.6. MH at 1 x 10(-3) M without S-9 mix inhibited cell multiplication at pH 7.6, but did not cause a significant increase in SCE/cell. No interactions were noted between MH (2 x 10(-4) M) and S-9 mix nor between MH and pH levels tested. Results indicate that in the presence of metabolic activation, SCE formation in human diploid fibroblasts in vitro may be used as a potential assay for mutagenicity. (35 Refs)

18. EFFECT OF CAFFEINE ON CELL KILLING, MUTATION INDUCTION, DNA REPAIR, AND DNA SYNTHESIS AFTER TREATMENT WITH ETHYLNITROSOUREA.

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Lab. Radiobiology, Univ. California, San Francisco, CA, 94143
Carcinogenesis; 2(12):1267-1271 1981

The effect of caffeine on cell killing, mutation induction, DNA repair, and inhibition of DNA synthesis was investigated in a clonal derivative of M3-1 Chinese hamster cells after treatment with N-ethyl-N-nitrosourea (ENU). Caffeine enhanced cell killing but had no effect on the mutation frequency/ viable cells for the two genetic markers, 6-thioguanine resistance and ouabain resistance. The removal of ethylated purine bases from DNA was as follows: most of the 3-ethyladenine was lost in 20 hr (greater than 85%) and approx 45% of the 7-ethylguanine was lost in 45 hr, whereas 75-93% of the O6-ethylguanine was still present at this time. Caffeine did not seen to influence these rates significantly. The ENU-induced inhibition of DNA synthesis was reversed by caffeine. It is concluded that the potentiation of ENU-induced cell killing by caffeine is caused by the increased frequency of DNA replication past damaged sites in parental DNA. (Author abstract) (25 Refs)

19. AGE-RELATED CHANGES IN MUTAGEN ACTIVATION BY RAT TISSUES.

Robertson IG, Birnbaum LS
(c/o Birnbaum) Environmental Biology Branch, Natl. Inst. Environmental Health Sciences, P.O. Box 12233, Research Triangle Park, NC, 27709
Chem Biol Interact; 38(2):243-252 1982

Age-related changes in drug metabolism of the liver, lung and kidney of adult female Long-Evans rats were determined by measuring changes in mutagen formation. Activation of aflatoxin B1 (AFB1), 2-aminofluorene (AF) and 2-acetylaminofluorene (AAF) to mutagenic derivatives was assayed using the Ames Salmonella test system. The promutagens were incubated with tissue fractions from rats ranging in age from 2.5 to 25 mo. With all three compounds, hepatic, renal and pulmonary activation was lower in the senescent than in the young adult animals. The largest decrease, however, occurred prior to middle-age, ie before 9-13 mo. In liver and kidney, little change was detectable between the middle-aged and the old (20-25 mo) animals. However, pulmonary metabolism in the oldest animals was slightly higher than in the extracts from the middle-aged rats. The observed decline in mutagen activation may thus be a function of maturation rather than senescence. (Author abstract) (30 Refs)

20. POLYCYCLIC AROMATIC HYDROCARBONS AND POSSIBLE METABOLITES: CONVERTOGENIC ACTIVITY IN YEAST AND TUMOR INITIATING ACTIVITY IN MOUSE SKIN.

Siebert D, Marquardt H, Friesel H, Hecker E
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J Cancer Res Clin Oncol; 102(2):127-139 1981

The diploid respiratory-deficient strain of yeast D4-RDII was used to assay PAH and urethane as well as some oxygenated derivatives of PAH and the (aliphatic) epoxide hydrolase inhibitor TCPO for convertogenic (mutagenic) activity. As a positive control, the convertogenic ultimate rat liver carcinogen NOAcAAF was used. PAH and urethane were found inactive as convertogens, TCPO was weakly active, whereas oxygenated electrophilic derivatives of PAH, such as K-region oxides, were found strong convertogens. For comparison, some convertogenic key compounds were assayed for their tumor-initiating activity in mouse skin in the standardized system using TPA as a promoter. PAH were stronger initiators than all oxygenated derivatives of PAH tested. TCPO alone exhibited very weak, if any, initiating activity. It was unable to modify initiation to any significant extent, if administered 5 min prior to administration of an initiator. In the absence of correlation between convertogenic and initiating activity the question of the chemical nature of 'ultimate initiators' of mouse skin carcinogenesis awaits further investigation. (Author abstract) (35 Refs)

21. IN VITRO MUTAGENIC ACTIVATION OF 3'-HYDROXY-METHYL-N,N-DIMETHYL-4-AMINOAZOBENZENE (3'-CH2OH-DAB) (MEETING ABSTRACT).

Mori Y, Niwa T, Toyoshi K
Gifu University, Gifu, Japan
Proceedings of the Japanese Cancer Association, 40th Annual Meeting, October 1981, Sapporo, Japan. The Association 415 pp., 1981.

Our earlier experiment indicates that 3'-CH2OH-DAB, a new potent hepatocarcinogen, showed mutagenic activity towards Salmonella typhimurium TA-98 and 100 when tested with S-9. In order to clarify the mechanism of metabolic activation by S-9, effects of various factors known to influence xenobiotics metabolism on the mutagenic activities of 3'-CH(2)0H-DAB and 3'-Me-DAB were studied. The pretreatment of rats with polychlorinated biphenyl (PCB) and 3-methylcholanthrene (3-MC) and sodium phenobarbital (PB) showed that the ability of S-9 to activate these compounds was induced to the highest extent by PCB followed by 3-MC and PB, and the activation reaction required NADPH as a cofactor. On the other hand, these compounds showed less or no mutagenic activity in the presence of the S-105 fraction or S-9 from the livers of non-treated rats, those of mice and hamsters, and other organs of rats. These results indicate that microsomal enzymes in the S-9 fraction of rat liver is responsible for the metabolic activation of 3'-CH(2)0H-DAB and 3'-Me-DAB and that the carcinogenic specificity in regard to organs and species is similarly observed in their mutagenic effects with S-9. (no Refs)

22. RELATIVE CONCENTRATIONS OF POLYAROMATIC PRIMARY AMINES AND AZAARENES IN MUTAGENICALLY ACTIVE NITROGEN FRACTIONS FROM A COAL LIQUID.

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Mutat Res; 90(4):321-335 1981

Relative concentrations of polyaromatic primary amines (PAA) and azaarenes (AA) were measured in various fractions of the process solvent (PS) from a solvent refined coal process. Fractions of PS were obtained by thin-layer chromatography. Mutagenic activity (MA) was determined in Salmonella typhimurium TA98. All detectable MA was indirect, requiring metabolic activation by S9 enzymes prepared from Wistar rat liver homogenates. MA of the neutral tar and basic fractions of PS was approx proportional to the concentration of PAA in those fractions. MA of the basic tar fraction was greater than expected from PAA concentration, possibly because of large amounts of material not detectable by gas-liquid chromatography. AA were found in mutagenic and nonmutagenic fractions of PS. Data suggest that AA having 2-4 fused rings are not major contributors to the MA of PS. In the basic fraction 2-and 3-ring PAA predominated; 4-ring PAA were present in lower concentrations. In the neutral and basic tar fractions 4-ring PAA predominated; 3-ring PAA were present in lower concentrations and 2-ring PAA were present only in trace amounts. Results indicate that PAA are present in PS; the presence of PAA corresponds to MA of PS and its component fractions. (15 Refs)

23. EFFECT OF AROMATIC HYDROCARBONS ON THE METABOLISM OF 2-AMINOANTHRACENE TO MUTAGENIC PRODUCTS IN THE AMES ASSAY.

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Bureau Veterinary Medicine, Food and Drug Admin., Beltsville, MD, 20705

Carcinogenesis; 2(12):1367-1369 1981

When the carcinogen 2-aminoanthracene was tested for mutagenicity in the Ames assay, the inclusion of aromatic hydrocarbons of various ring sizes had differing effects on mutagenicity depending on the components of the assay. (Author abstract) (16 Refs)

24. THE EFFECT OF TESTOSTERONE TREATMENT ON THE ABILITY OF FEMALE RAT LIVER S9 TO ACTIVATE AFLATOXIN B1 AND 2-AMINOFLUORENE IN THE AMES/SALMONELLA SYSTEM.

Chernesky P, Jayaraj A, Richardson A
Dept. Chemistry, Illinois State Univ., Normal, IL, 61761
Mutat Res; 103(3-6):267-273 1982

The activation of aflatoxin B1 (AFB1) and 2-aminofluorene (2AF) by liver homogenates (S9) from untreated and testosterone-treated female Fischer F344 rats was compared using the Ames Salmonella (TA98)/microsome assay. Testosterone treatment resulted in a 93% increase in the ability of S9 to convert AFB1 to mutagenic compounds in the Ames test and a 43% increase in the similar activation of 2AF. (21 Refs)

25. EFFECTS OF ORTHO-METHYL SUBSTITUENTS ON THE MUTAGENICITY OF AMINOBIPHENYLS AND AMINONAPHTHALENES.

El-Bayoumy K, LaVoie EJ, Tulley-Freiler L, Hecht SS
Naylor Dana Inst. Disease Prevention, American Health Foundation, Valhalla, NY, 10595
Mutat Res; 90(4):345-354 1981

Mutagenic activity (MA) of five aminobiphenyls and five aminonaphthalenes was studied in Salmonella typhimurium strains TA100, TA1535, and TA1538 using the Ames assay. Metabolic activation was provided by S9 mix prepared from the livers of male Fischer-344 rats treated with Aroclor. MA was observed only in the presence of S9. Of the aminobiphenyls only 4-aminobiphenyl (4ABP) showed MA; 4ABP was active against TA1538 and TA100 but not against TA1535. 4-amino-3-methylbiphenyl (4A3M) showed greater MA than 4ABP against TA1538; 3-amino-4-methylbiphenyl (3A4M) and 3-aminobiphenyl (3ABP) showed no MA against TA 1538. 3A4M showed MA against TA100, while 3ABP did not. Results indicate that the presence of an ortho-methyl group enhances the MA of aminobiphenyls. Among the 2-aminonaphthalenes 2-amino-3-methylnaphthalene (2A3M) had the greatest MA against TA1538, followed by 2-amino-1-methylnaphthalene (2A1M) and 2-aminonaphthalene (2AN). 2AN had the greatest MA against TA1535. Neither 1-aminonaphthalene (1AN) nor 1-amino-2-methylnaphthalene had any MA against TA1538 or TA1535. 1AN showed weak MA against TA100. Results indicate that the presence of an ortho-methyl group inhibits base-pair MA and enhances frame-shift MA in aminonaphthalenes. (22 Refs)

26. IN VIVO AND IN VITRO STUDY OF MUTAGENICITY OF CARCINOGENIC N-NITRAMINES.

Khudolei VV, Malaveille C, Bartsch H
N. N. Petrov Res. Inst. Oncology, USSR Ministry Health, Leningrad, USSR
Vopr Onkol; 27(11):59-62 1981

The mutagenicity of dimethylnitramine, diethylnitramine and nitromorpholine was established in host-mediated assay with Salmonella typhimurium TA 1530 as indicator organism. It was demonstrated in experiments involving isolation of the bacteria from liver that enzymatic activation is required for bringing about the mutagenic effect of diethylnitramine. In in vitro experiments it was shown that carbonium cation is responsible for the carcinogenic and mutagenic effects of nitramines. (Author abstract) (11 Refs) (In RUS)

27. MUTAGENICITY OF AMINOCARBAZOLES AND NITROCARBAZOLES.

LaVoie EJ, Govil A, Briggs G, Hoffmann D
Div. Environmental Carcinogenesis, Naylor Dana Inst. Disease Prevention, American Health Foundation, Valhalla, NY, 10595
Mutat Res; 90(4):337-344 1981

Mutagenic activity (MA) of the C-substituted nitro and amino derivatives of carbazole was studied in Salmonella typhimurium TA98 and TA100 using the Ames assay. As a metabolic activation system, S9 preparations were obtained from rats treated with Aroclor. Bacterial cultures were exposed to nitrocarbazoles (1, 2, 5, 10, 25, 50, 100, or 200 ug/plate) or aminocarbazoles (5, 10, 25, 50, 100, or 200 ug/plate). In the absence of S9, 2-nitrocarbazole (2NC) and 3-nitrocarbazole (3NC) were mutagenic towards TA98 cultures, while 1-nitrocarbazole (1NC) and 4-nitrocarbazole (4NC) were not. 2NC had MA similar to that of 2-nitrofluorene. In the presence of S9 the MA of 2NC and 3NC was reduced, 4NC showed weak MA, and 1NC remained inactive towards T98. 1NC and 3NC showed no MA towards TA100 with or without S9. 4NC showed MA towards TA100 with or without S9. 2NC showed weak MA with S9. All aminocarbazoles showed greater MA with S9 than without S9. 1-Aminocarbazole was inactive towards both TA98 and TA100. MA of 2-aminocarbazole was greater than that of 2-aminofluorene (2AF) without S9 and less than that of 2AF with S9. 3-Aminocarbazole showed moderate MA towards TA98 with S9 but no MA towards TA100. 4-Aminocarbazole showed MA towards TA100 but only marginal MA towards TA98. Because none of the test compounds showed MA towards the exclusive base pair tester strain TA1535, specificity in base pair or frame shift mechanism of action between isomers could not be confirmed. (15 Refs)

28. THE MUTAGENICITY OF DINITROTOLUENES IN SALMONELLA TYPHIMURIUM.

Couch DB, Allen PF, Abernethy DJ
Dept. Genetic Toxicology, Chemical Industry Inst. Toxicology, P.O. Box 12137, Res. Triangle Park, NC, 27709
Mutat Res; 90(4):373-383 1981

Mutagenic activity (MA) of the six isomers of dinitrotoluene individually and in a mixture was studied using three assays with Salmonella typhimurium strains TA1535, TA1537, TA1538, TA98, TA100, and TM677. Metabolic activation was provided by microsomal preparations (PMS) from F-344 rats treated with Aroclor. S typhimurium were exposed to 2,3-dinitrotoluene (2,3-DNT), 2,4-dinitrotoluene (2,4-DNT), 2,5-dinitrotoluene (2,5-DNT), or 3,4-dinitrotoluene (3,4-DNT) (all at 200 ug/plate), 2,6-dinitrotoluene (2,6-DNT: 1,000 ug/plate), 3,5-dinitrotoluene (3,5-DNT: 40 ug/plate) or technical grade 2,4-DNT (TG). TG contained 76.5% 2,4-DNT, 18.8% 2,6-DNT, and small amounts of the other isomers. All samples tested showed MA in the Ames Salmonella/microsome test. The presence of PMS generally reduced MA of test compounds. MA was greatest in strains sensitive to frame-shift mutagens. 3,5-DNT had the greatest MA in inducing reversions to histidine prototrophy in strains TA98 and TA1538, as well as in a quantitative reversion assay in TA98. All samples tested increased the 8-azaguanine-resistant fraction of TM677 in a forward mutation assay; 3,5-DNT did not exceed the other isomers in MA in this assay. (19 Refs)

29. THE MUTAGENIC POTENTIAL OF 4 NITROPHENYL BIS(2-THIENYL)-PHOSPHINATE; 4-NITROPHENYL 2-FURYL(METHYL)-PHOSPHINATES; 4-CYANOPHENYL BIS(2-FURYL)-PHOSPHINATE; 4-NITROPHENYL BIS(2-FURYL)-PHOSPHINATE.

Sauers LJ, Pulliam FR, Fruin JT
Letterman Army Inst. Res., San Francisco, CA
The Mutagenic Potential of 4 nitrophenyl bis(2-thienyl)-phosphinate; 4-nitrophenyl 2-furyl(methyl)-phosphinates; 4-cyanophenyl bis(2-furyl)-phosphinate; 4-nitrophenyl bis(2-furyl)-phosphinate. Available from National Technical Information Service, Springfield, VA, as ADA105 978/1:, 37 pp., 1981.

The mutagenic potential of 4 nitrophenyl bis(2-thienyl)phosphinate; 4-nitrophenyl 2-furyl(methyl)phosphinate 4 cyanophenyl bis(2-furyl)phosphinate; 4-nitrophenyl bis(2-furyl)phosphinate was assessed by using the Ames Salmonella/Mammalian Microsome Mutagenicity Assay. Tester strains TA 98, TA 100, TA 1535, TA 1537 and TA 1538 were exposed to doses ranging from 1 mg/plate to 0.00032 mg/plate. It was determined that none of the tested substances had mutagenic potential. (Author abstract)

30. URINARY METABOLITES OF 3,3'-DICHLOROBENZIDINE AND THEIR MUTAGENICITY.

Tanaka KI
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Sangyo Igaku; 23(4):426-427 1981

3,3'-dichlorobenzidine (DCBZ) was administered to rats, urinary metabolites of the DCBZ, 3,3'-dichloro-N-acetylbenzidine (N-AcDCBZ) and 3,3'-dichloro-N,N'-diacetylbenzidine (NN'-AcDCBZ), were observed in the urine of the rats, and mutagenicity of the DCBZ, N-AcDCBZ, and NN'-AcDCBZ was investigated using Salmonella typhimurium TA 98 and TA 100 and a revertant mutagenicity test. Spectrographic pure DCBZ was administered po (20 mg) to five rats (Group 1), per trachea (10 mg) to five (Group 2), and sc (200 mg) to five (Group 3); five rats were not administered the DCBZ. DCBZ, N-AcDCBZ, and NN'-AcDCBZ were detected with both gas chromatography and high pressure liquid chromatography in the urine of Group 1 and 2 rats. Only NN'-AcDNBZ was observed in the urine of Group 3 rats. With the aid of Ames test, mutagenic activity of 1 ml urine samples containing N-acetyl DCBZ metabolites was shown to increase with the concentration of the metabolites in the urine samples from the Group 1 and 2 rats, but no mutagenic activity was observed for the 1 ml samples from the Group 3 rats. The mutagenic activity of the NN'-AcDCBZ was much lower than that of the DCBZ or the N-AcDCBZ. These techniques were thought to be applicable for study of mechanisms of carcinogenicity of these metabolites as well as for biological monitoring of the substances. (7 Refs) (In JPN)

31. EVALUATION OF 4-HYDROXYMETHYLBIPHENYL (4HMB), 4-CHLOROMETHYLBIPHENYL (4CMB) AND BENZYL CHLORIDE (BC) USING THE AMES SALMONELLA/MICROSOME INCORPORATION TEST FOR MUTAGENICITY.

Moore WB, Chatfield SN
Dept. Bacteriology, Wellcome Res. Lab., Langley Court, Beckenham, Kent BR3 3BS, England
Mutat Res; 100(1-4):35-38 1982

Abilities of 4-chloromethylbiphenyl (4CMB), benzyl chloride (BC), and 4-hydroxymethylbiphenyl (4HMB) to effect point mutations at histidine loci in each of five specially constructed strains of Salmonella typhimurium (TA1535, TA1537, TA1538, TA98, and TA100) were determined in vitro using the Ames Salmonella/microsome incorporation test. The results indicated that 4HMB is neither a direct nor pro-mutagen, 4CMB is a direct mutagen, and BC is a direct mutagen of low potency. (3 Refs)

32. THE MUTAGENIC ACTIVITY OF 4-CHLOROMETHYLBIPHENYL (4CMB) AND BENZYL CHLORIDE (BC) IN THE BACTERIAL/MICROSOME ASSAY.

Brooks TM, Gonzalez LP
Sittingbourne Res. Centre, Shell Res. Ltd., Sittingbourne, Kent, ME9 8AG, England
Mutat Res; 100(1-4):61-64 1982

The mutagenic activity of 4-chloromethylbiphenyl (4CMB) was studied in agar layer cultures of Salmonella typhimurium TA1535, TA1537, TA1538, TA98, and TA100, and Escherichia coli WP2 and WP2uvrA. The mutagenic activity of benzyl chloride (BC) was investigated in only Salmonella strains. Assays were performed with or without S9 activation. The results indicated that 4CMB is a direct-acting bacterial mutagen that shows a greater response in strains TA1538 and TA98, and that this activity is reduced in the presence of the S9 fraction. BC is a bacterial mutagen in strain TA100 only and the mutagenic response is increased by S9 mix. (4 Refs)

33. MUTAGENICITY OF 4-CHLOROMETHYLBIPHENYL IN THE SALMONELLA/MICROSOME ASSAY.

Pagano DA, Shelby MD
Natl. Inst. Environmental Health Sciences, Triangle Park, NC, 27709
Mutat Res; 100(1-4):67-70 1982

The mutagenic activity of 4-chloromethylbiphenyl (4CMB) was determined in Salmonella typhimurium strains TA1535, TA1537, TA98, and TA100 using the plate incorporation assay with and without rat-liver S9. 4CMB was positive in strains TA1537, TA98, and TA100 both with and without S9 activation. A weakly positive response was seen with strain TA1535 tested without activation. (4 Refs)

34. MUTAGENICITY OF 4-CHLOROMETHYLBIPHENYL IN REPAIR-DEFICIENT STRAINS OF SALMONELLA TYPHIMURIUM.

Forster R
Water Res. Centre, Henley Road, Medmenham, Marlow, Bucks SL7 2HD, England
Mutat Res; 100(1-4):75-79 1982

The mutagenic activity of 4-chloromethylbiphenyl (4CMB) was examined in a series of repair deficient derivatives of Salmonella typhimurium LT2 using the fluctuation test. 4CMB was mutagenic to frameshift tester strains at 0.01-50 ug/ml, except in genetic backgrounds; no mutagenicity was observed in base-pair substitution tester strains at the dose levels used, except in the presence of the plasmid pKM101. Thus 4CMB appears to be primarily active as a frameshift mutagen. A much greater effect was seen in the excision-deficient strain TA1533 than in the repair wild-type strain D3052, suggesting that 4CMB forms an excisable DNA adduct. Increased cellular permeability resulting from the 'deep rough' (rfa) mutation led to greater mutation production by 4CMB, as can be seen by comparison of results for strains TA1533 and TA1538 which are isogenic except for the rfa mutation in TA1538. Strain TS27, which carries the recA allele and is completely deficient in recombination and error-prone repair, was almost as sensitive to

4CMB mutation as D3052; such a result suggests that a substantial proportion of the frameshift activity of 4CMB is independent of rec-lex function, consistent with the finding that the plasmid pKM101 has no observable effect on frameshift mutation by 4CMB and strains TA98 and TA1538 are equally sensitive to 4CMB mutation. The mechanism of 4CMB mutagenesis is discussed. (14 Refs)

35. FLUCTUATION TEST DATA ON 4-CHLOROMETHYLBIPHENYL (4CMB), 4-HYDROXYMETHYLBIPHENYL (4HMB) AND BENZYL CHLORIDE (BC) USING SALMONELLA TYPHIMURIUM TA98 AND TA100.

Sargent AW, Regnier AP
British Petroleum Res. Centre, British Petroleum Co. Ltd., Chertsey Road, Sunbury-on-Thames, Meddx. TW16 7LN, England
Mutat Res; 100(1-4):87-90 1982

Bacterial fluctuation tests were performed with and without metabolic activation using the Ames Salmonella typhimurium strains TA98 and TA100. The mutagenic potential of benzyl chloride, 4-chloromethylbiphenyl (4CMB), 4-hydroxymethylbiphenyl (4HMB), and benzyl chloride (BC) was assayed. 4CMB was mutagenic both with and without metabolic activation in TA100 and TA98. Data for 4HMB was negative. BC was non-mutagenic. (4 Refs)

36. THE GENETIC TOXICOLOGY IN FUNGI OF 4-CHLOROMETHYLBIPHENYL (4CMB), 4-HYDROXYMETHYLBIPHENYL (4HMB) AND BENZYL CHLORIDE (BC). SURVEY OF THE RESULTS OF THE U.K.E.M.S. COLLABORATIVE GENOTOXICITY TRIAL 1981.

Parry JM, Wilcox P
Dept. Genetics, Univ. Coll. Swansea, Swansea SA2 8PP, Wales
Mutat Res; 100(1-4):185-200 1982

The genetic toxicology of 4-chloromethylbiphenyl (4CMB), 4-hydroxymethylbiphenyl (4HMB), and benzyl chloride (BC) has been studied in Saccharomyces cerevisiae, Aspergillus nidulans and Neuropsora crassa. Both 4CMB and BC are potent mutagens for nuclear genes in N crassa. No conclusions have been drawn about the abilities of any of the three compounds to induce point mutations in A nidulans. Both 4CMB and BC are potent inducers of mitotic gene conversion and mitotic crossing-over in fungi. 4CMB and BC are able to induce mitotic crossing-over in both yeast and A nidulans; no such activity has been detected with 4HMB. 4CMB has appeared to be a potent point mutagen in S cerevisiae. 4HMB is effective in inducing mitochondrial mutations and inhibiting the activity of mitochondrial genome. Results of studies on the effects of BC and 4CMB on the mitochondrial genome have been variable. Overall, the results of fungal assays have indicated that both 4CMB and BC are genetically active chemicals; no such activity has been detectable with 4HMB. (17 Refs)

37. THE INDUCTION OF MUTANTS IN L5178Y MOUSE LYMPHOMA CELLS BY 4-CHLOROMETHYLBIPHENYL.

Arlett CF, Muriel WJ, Cole J, Lowe J
MRC Cell Mutation Unit, Univ. Sussex, Falmer, Brighton, Sussex BN1 9QG, England
Mutat Res; 100(1-4):253-256 1982

The mutagenicity of 4-chloromethylbiphenyl (4CMB) was assessed in L5178Y mouse lymphoma cells by measuring the appearance of mutant cells resistant to various metabolic inhibitors. At a concentration of 50 ug/ml, 4CMB produced significant dose-dependent induction of resistance to methotrexate and 1-beta-D-arabinofuranosylcytosine; induction of resistance to 6-thioguanine was dose-related but not significant. 4CMB was not mutagenic with respect to ouabain resistance. (6 Refs)

38. THE EFFECTS OF 4CMB, 4HMB, AND BC ON SCE, CHROMOSOME ABERRATION AND POINT MUTATION IN CULTURED CHINESE HAMSTER OVARY CELLS.

Phillips BJ, James TE
British Industrial Biological Res. Assoc., Woodmansterne Road, Carshalton, Surrey SM5 4DS, England
Mutat Res; 100(1-4):263-269 1982

Mutagenicity of 4-chloromethylbiphenyl (4CMB), 4-hydroxymethylbiphenyl (4HMB), and benzyl chloride (BC) was studied in vitro in Chinese hamster ovary (CHO-KI-BH4) cells in the absence of exogenous metabolic activation systems. CHO-KI-BH4 cells were exposed to 4CMB, 4HMB, or BC for 2 hr. Tests of relative plating efficiency indicated that 4HMB is nontoxic at concentrations up to 100 ug/ml; above 100 ug/ml 4HMB precipitated from soln. 4CMB was slightly more toxic than BC. Sister chromatid exchanges (SCE) were significantly increased by BC in a dose-related manner; the max effect of 4CMB was a doubling of the background frequency of SCE at a concentration of 7 ug 4CMB/ml; 4HMB had no effect on the frequency of SCE. 4CMB produced moderate but significant chromosomal aberrations (CA) within a concentration range of 10-20 ug/ml; BC produced somewhat more CA but at higher doses than 4CMB. 4HMB produced no effect on CA. 4CMB produced a slight increase in the frequency of cell mutations (CM) within a narrow range of doses around 10 ug/ml. BC produced a small increase at a dose of 18 ug/ml, and 4HMB had no effect on CM. Results indicate that 4CMB and BC are weakly mutagenic in the absence of an exogenous metabolic activation system. SCE, CA, and CM test results agreed quantitatively and qualitatively. (4 Refs)

39. CHROMOSOME ANALYSIS OF CULTURED RAT-LIVER EPITHELIAL CELLS (RL4) TREATED WITH 4-CHLOROMETHYLBIPHENYL, 4-HYDROXYMETHYLBIPHENYL AND BENZYL CHLORIDE.

Malallah G, Danford N, Parry JM
Genetic Toxicology Group, Univ. Coll. Swansea, Swansea SA2 8PP, Wales
Mutat Res; 100(1-4):279-282 1982

Induction of chromosomal aberrations by 4-chloromethylbiphenyl (4CMB), 4-hydroxymethylbiphenyl (4HMB), and benzyl chloride (BC) was studied in rat-liver epithelial cells of the line RL4, which retains some metabolic activation. Cytotoxicity was determined by seeding 50,000 cells/well onto culture plates, culturing for 24 hr, and then exposing the cells to a test chemical for 24 hr. The concentration of test chemical producing 50% inhibition of cell growth (GI50) was calculated for each chemical. Genotoxicity assays were conducted using 25, 50, 75, and 100% of the GI50. Cell cultures were exposed for 24 hr to 6, 12, 18, or 24 ug 4CMB/ml, 25, 50, 75, or 100 ug 4HMB/ml, or 7.5, 15, 22.5, or 30 ug BC/ml. Both 4CMB and BC produced significant increases in chromosomal aberrations at doses that were only slightly toxic to RL4 cells. Sixty uM 4CMB produced approx 6x as much damage as 60 uM BC; 120 uM 4CMB produced greater than 10x as much damage as 120 uM BC. 4CMB produced 3x as much chromosome damage as equitoxic concentrations of BC. No clear effects on chromosome number were noted, except an increase in the number of cells with 43 or fewer chromosomes at 18 or 24 ug/ml 4CMB. Since no increase was observed in the number of cells with 46 or more chromosomes, 4CMB apparently does not cause nondisjunction. 4HMB produced no chromosomal aberrations. Results indicate that 4CMB and BC are clastogenic and 4CMB has the greater activity. (1 Ref)

40. UKEMS COLLABORATIVE GENOTOXICITY TRIAL: CYTOGENETIC TESTS OF 4CMB, BC AND 4HMB: SUMMARY AND APPRAISAL.

Scott D
Paterson Lab., Christie Hosp., Manchester M20 9BX, England
Mutat Res; 100(1-4):313-331 1982

Studies of the genotoxic potential of 4-chloromethylbiphenyl (4CMB), 4-hydroxymethylbiphenyl (4HMB), and benzyl chloride (BC) in vitro and of 4CMB in vivo are reviewed. Trials used eight different systems (cultured rat-liver epithelial cells, Chinese hamster V79 and bone marrow cells, human lymphocytes and fibroblasts, and mouse bone marrow cells in vitro, and mouse spermatocytes and oocytes in vivo). Aberrations in chromosomal structure (CA) and sister chromatid exchanges (SCE) were produced by 4CMB and BC but not 4HMB. No consistent differences in effectiveness were found between 4CMB and BC. Changes in chromosome number were not produced by any of the test compounds. 4CMB produced greater increases in CA and SCE in the presence of metabolic activation systems (in rat liver epithelial cells or in the presence of S9 mix) than in the absence of such systems. Since 4CMB does not require activation, the findings suggest that under certain conditions 4CMB can be converted to a more potent electrophile. Overall results indicate that 4CMB is a weak mutagen. (16 Refs)

41. GENETIC ACTIVITIES OF 4-CHLOROMETHYLBIPHENYL, THE 4-HYDROXY DERIVATIVE AND BENZYL CHLORIDE IN THE SOMA AND GERM LINE OF DROSOPHILA MELANOGASTER.

Fahmy MJ, Fahmy OG
Dept. Genetics, Inst. Cancer Res., Pollard Woods Res. Station, Chalfont St. Giles, Buckinghamshire HP8 4SP, England
Mutat Res; 100(1-4):339-344 1982

Induction of alterations in gene expression by 4-chloromethylbiphenyl (CMB), 4-hydroxymethylbiphenyl (4HMB), and benzyl chloride (BC) was studied in the soma and germ line of Drosophila melanogaster. Late embryos and newly hatched larvae were exposed to the test compounds in concentrations up to 2 milliM (mM) until maturation. Somatic alterations were measured by determining alterations in expression of the unstable w+ locus in mature treated males. At 0.5-2.0 mM, 4CMB, 4HMB, and BC increased the frequency of red eye sectors resulting from repression or deletion of the zeste-regulatory proximal subunits of the w+ locus. 4CMB and 4HMB had approx the same activity, while BC had an activity approx twice that of the other two compounds. At 0.5-2.0 mM concentrations 4HMB and BC each increased the frequency of occurrence of white eye sectors resulting from deletions within the structure of the w+ locus by approx one order of magnitude relative to untreated controls. 4CMB did not affect the occurrence of white sectors. Red sectors had a mean size of 27 +-6 ommatidia, corresponding to an eye anlage size of approx 30 cells at the time of induction. White sectors had a mean size of 87 +-17 ommatidia, corresponding to an eye anlage size of 9 cells at the time of induction. These findings indicate that induction of red sector occurred at or after the time of genetic determination during eye differentiation. The test compounds are apparently weak mutagens in the order 4CMB less than or equal to 4HMB less than or equal to BC. (5 Refs)

42. THE GENETIC TOXICOLOGY OF 4-CHLOROMETHYLBIPHENYL (4CMB), 4-HYDROXYMETHYLBIPHENYL (4HMB), AND BENZYL CHLORIDE (BC) AS ASSESSED BY THE UKEMS GENOTOXICITY TRIAL (1981).

Parry JM
Dept. Genetics, Univ. Coll. Swansea, Swansea SA2 8PP, Wales
Mutat Res; 100(1-4):411-416 1982

Studies of the genetic toxicology of 4-chloromethylbiphenyl (4CMB), 4-hydroxymethybiphenyl (4HMB), and benzyl choride (BC) are reviewed. Bacterial studies showed that 4CMB is a strong, direct-acting mutagen. 4CMB produces frame-shift and base-pair mutations, apparently by different mechanisms. In fungi 4CMB produced point mutations, mitotic gene conversions, primary DNA damage, and mitotic crossing-over; the presence of metabolic activation systems (MAS) reduced overall toxicity without affecting genetic effects of 4CMB. In mammalian cell cultures 4CMB produced repairable DNA damage, point mutations, chromosome aberrations, and sister chromatid exchanges. In vivo studies did not show that 4CMB induces dominant lethal mutations, micronuclei, aberrations of sperm morphology, or skin tumors. Initial findings suggest that 4CMB may be a weak skin carcinogen. Bacterial studies showed BC to be mutagenic with approx 10% of the base-pair substitution activity of 4CMB. The mutagenic activity of BC increased in the presence of MAS. In fungi BC had mutagenic activity similar to 4CMB. In mammalian cell cultures BC had approx 20% of the activity of 4CMB. No evidence of skin carcinogenicity has been found after 10 mo. No evidence for mutagenicity of 4HMB was found in any system tested. Overall results indicate the value of a range of tests in determining genetic toxicology of compounds. (8 Refs)

43. AN OVERVIEW OF THE CHEMICAL AND BIOLOGICAL REACTIVITY OF 4CMB AND STRUCTURALLY RELATED COMPOUNDS: POSSIBLE RELEVANCE TO THE OVERALL FINDINGS OF THE UKEMS 1981 STUDY.

Ashby J, Lefevre PA, Elliott BM, Styles JA
Central Toxicology Lab., Imperial Chemical Industries Ltd., Alderley Park, Macclesfield, Cheshire, England
Mutat Res; 100(1-4):417-433 1982

Negative mutagenicity results for 4-chloromethylbiphenyl (4CMB) obtained during collaborative studies are discussed. Topics include bacterial mutagenicity of 4CMB with respect to structurally-related analogs of biphenyl, metabolic detoxification of 4CMB, the effect of 4CMB on thermal denaturation of calf thymus DNA, hydrolysis of 4CMB to 4-hydroxymethylbiphenyl (4HMB), activity of 4CMB relative to benzyl chloride (BC), detoxification of 4CMB by 'non-critical' macromolecules, and derivatives of 4CMB with altered chemical stability. Addition of a benzene ring to BC to yield 4CMB is apparently accompanied by a marked increase in genotoxic activity in vitro and a decrease in hydrolytic stability, such that 4CMB may be quickly transformed into 4HMB. Awareness of the hydrolytic stability of a new alkylating agent and knowledge of its aqueous/lipid partition coefficient, its stability in S9, and responses observed in a variety of modifications of the Salmonella assay are required for estimation of genotoxic potency in vivo. (19 Refs)

44. MUTAGENICITY OF DIPHENYLHYDANTOIN AND SOME OF ITS METABOLITES TOWARDS SALMONELLA TYPHIMURIUM STRAINS.

Sezzano P, Raimondi A, Arboix M, Pantarotto C
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Mutat Res; 103(3-6):219-228 1982

The mutagenicity of 5,5-diphenyl-hydantoin (DPH) and its major metabolite 5-(4-hydroxyphenyl)-5-phenylhydantoin (HPPH) were tested in vitro using S typhim urium strains T1535, TA 100, TA 1537, TA 1538 and TA 98. Neither DPH nor HPPH alone was mutagenic or cytotoxic at doses ranging from 1-1000 ug/plate. When mutagenicity was tested in the presence of liver S9 fraction from rats pretreated with different cytochrome P-450/448 inducers (corn oil; phenobarbital (PB)); beta-naphthoflavone; 3-methylcholanthrene 3-MC; Aroclor 1254, (PCB), DPH at concentrations of 25 ug/plate with 3-MC and 250 ug/plate with PCB pretreated rat S9 had limited mutagenic activity in strain TA 1538. Significant increases in revertant colonies were found with HPPH tested on strains TA98, TA1535, TA1537, and TA1538 when in the presence of S9 from BNF-, 3MC- and especially PCB-pretreated rats. These results are further supported by metabolic studies, which showed that HPPH and the other DPH metabolite 5-(3,4-dihydroxyphenyl)-5-phenylhydantoin (DHP) were formed when incubation of DPH was done in S9 fractions from livers of rats pretreated with BNF, 3MC or PCB, but not PB. Epoxide intermediates in the metabolism of DPH to HPPH and to HPPH to DHP may be responsible for the mutagenicity. A reaction mechanism is proposed. (21 Refs)

45. MUTAGENICITY OF THE ANTIPARASITIC DRUG VERMOX FOR SALMONELLA TYPHIMURIUM HISTESTER STRAINS.

Paulikova H, Dobias L
Regional Hygienic Inst., 728 92 Ostrava, Czechoslovakia
Mutat Res; 90(4):463-468 1981

Salmonella typhimurium strains TA100, TA98, TA1535, and TA 1538 were exposed to Vermox to test the mutagenicity (MG) of methyl-5(6)-benzoyl-2-benzimidazole carbamate, a component of Vermox. No MG as indicated by histidine prototrophic reversion was noted with or without metabolic activation by rat liver S9. Blood samples from rats treated with Vermox did not produce an increase in reversions, indicating that metabolic activation in vivo does not produce mutagenic activity. (11 Refs)

46. NEGATIVE RESULTS OF CARCINOGENICITY BIOASSAY OF METHYL CARBAZATE IN RATS: SIGNIFICANCE FOR THE TOXICOLOGICAL EVALUATION OF CARBADOX.

Truhaut R, Ferrando R, Faccini JM, Monro AM
(c/o Monro) Centre de Recherche, Laboratoires Pfizer, B.P. 109, 37401 Amboise Cedex, France
Toxicology; 22(3):219-221 1981

Carcinogenicity bioassay of methyl carbazate, a metabolite of carbadox, was conducted in Wistar rats. The highest dose level of methyl carbazate used in the study exceeds slightly the dose which could be released by complete metabolism of the lowest dose of carbadox shown to be tumorigenic. Results showed no evidence of any treatment-related toxicity or carcinogenicity for methyl carbazate. (4 Refs)

47. CHARACTERIZATION OF POLYCYCLIC KETONES AND QUINONES IN DIESEL EMISSION PARTICULATES BY GAS CHROMATOGRAPHY/MASS SPECTROMETRY.

Choudhury DR
Vick Div. Res. and Development, Richardson-Vicks Incorporated, 1 Bradford Road, Mount Vernon, NY, 10553
Environ Sci Technol; 16(2):102-106 1982

High-resolution gas chromatography/mass spectrometry was used to determine the chemical composition of two highly mutagenic subfractions of the neutral fraction of a diesel particulate extract. Diesel emission particulates were collected from a Volkswagon Rabbit by the dilution tunnel method and the two subfractions were isolated by silica gel chromatographic fractionation of the neutral extract. Of seven subfractions prepared, subfractions 4 and 5 had the highest specific mutagenicity in the Ames Salmonella mutagenesis assay, with subfraction 4 accounting for 52% of the direct-acting mutagenicity and subfraction 5, 13%. Both direct-acting mutagens and promutagens which required metabolic activation were found in the subfractions. Elution patterns suggested that the subfractions contained compounds more polar than parent and alkyl-substituted polycyclic aromatic hydrocarbons. Ketone, quinone, carboxaldehyde, and hydroxy derivatives and their alkyl homologues were characterized. The single largest family of compounds detected were 9-fluorenone and its C1-C4 alkyl homologues. The mutagenicity of most of the compounds identified is unknown. (18 Refs)

48. MUTAGENICITY AND CHEMICAL ANALYSIS OF ALIPHATIC AND AROMATIC FRACTIONS OF PRUDHOE BAY CRUDE OIL AND FUEL OIL NO. 2.

Ellenton JA, Hallett DJ
Dept. of the Environment, Wildlife Toxicology Div., Natl. Wildlife Res. Center, Ottawa, Ontario K1A OE7, Canada
J Toxicol Environ Health; 8(5/6):959-972 1981

Chemical analyses of aliphatic and aromatic fractions of Prudhoe Bay crude (PBC) oil and fuel oil number 2 and their potential mutagenicity were investigated. Fraction 1 of both oils exhibited no mutagenic activity. PBC oil fractions 3 and 4 and fuel oil number 2 fraction 4 produced weak mutagenic activity with metabolic activation. A significant increase in sister chromatid exchanges occurred after treatment with various concentrations of fraction 3 and 4 from each oil. These results indicate genetic activity residing in the polycyclic aromatic hydrocarbon containing fractions of the tested oils in both bacteria and mammalian cells. (20 Refs)

49. THE EFFECTS OF NITROUS ACID ON THE MUTAGENICITY OF TWO COAL LIQUIDS AND THEIR GENETICALLY ACTIVE CHEMICAL FRACTIONS.

Pelroy RA, Stewart DL
Pacific Northwest Lab., Richland, WA, 99352
Mutat Res; 90(4):297-308 1981

The mutagenicity of solvent refined coal (SRC) distillates and distillate fractions was studied in Salmonella typhimurium TA98 and TA100 using the Ames assay. Chemicals tested included SRC-II heavy distillate (HD), SRC-I process solvent (PS), basic tar and neutral tar fractions of HD and PS, and samples of these chemicals that had been treated with either HCl or HNO2. SRC samples dissolved in dimethyl sulfoxide or emulsified in HCl medium contained mutagens that required activation by S9 enzymes. Treatment of SRC samples with HNO2 reduced the observed mutagenicity. Mutagens detected after HNO_2 treatment were direct acting; mutagenicity of the substances was apparently decreased by S9 enzymes. HCl did not decrease the mutagenicity of SRC samples. In the absence of S9 enzymes, mutagenicity of SRC compounds was reduced by 73% for PS, 80% for PS basic and neutral tars, and at least 90% for other SRC samples, compared with untreated samples. In the presence of S9 enzymes all HNO_2-treated samples showed less than 10% of the mutagenicity of untreated samples. HNO_2 treatment did not reduce mutagenicity of the nonprimary aromatic amine polycyclic compounds phenanthridine, dimethylbenzacridine, benzo[a]pyrene, and 2-acetylaminofluorene. Results suggest that primary aromatic amines are the most important contributors to mutagenicity of SRC distillates in the Ames assay system. (21 Refs)

50. MUTAGENIC CHARACTERIZATION OF SYNTHETIC FUEL MATERIALS BY THE AMES/SALMONELLA ASSAY SYSTEM.

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Mutat Res; 90(4):309-320 1981

Mutagenicity of solvent refined coal (SRC) distillates from two pilot processes (SRC-I and SRC-II) was studied in Salmonella typhimurium TA98. Samples tested included SRC-II heavy (HD), medium, and light distillates and SRC-I process solvent (PS), wash solvent, and light oil. HD and PS contained high-mol wt, high-boiling point compounds; of the crude samples only HD and PS showed mutagenic activity (MA). Dose-response curves were approx linear for HD and PS at 1-10 ug/plate. All MA required metabolic activation by S9 enzymes. Analysis of fractions of PS and HD obtained by solvent fractionation showed that specific MA was high for basic fractions, intermediate for basic tar and neutral tar fractions, and low for acidic tar fractions. Neutral, aliphatic, and neutral polyaromatic hydrocarbon-enriched fractions showed little or no MA. Fractions of PS obtained after solvent extraction accounted for 125% of the MA of crude PS; fractions of HD accounted for 88% of the MA of crude HD. Although the basic fractions of PS and HD had the highest specific MA, the basic tar and neutral tar fractions contributed the greatest portion of overall MA because these fractions made up 50% of the total weight of crude PS and HD compared with 1% of the basic fractions. The basic fractions of PS and HD had MA comparable to that of benzo[a]pyrene but less than that of 2-aminoanthracene. (25 Refs)

51. GENOTOXICITY OF COCOA EXAMINED BY MICROBIAL AND MAMMALIAN SYSTEMS.

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Mutat Res; 103(3-6):275-281 1982

The bone marrow sister-chromatid exchange (SCE) test, performed with implanted 5-bromodeoxyuridine tablets; the micronucleus test performed with outbred 10 to 14 wk-old Chinese hamsters, and the Ames test with Salmonella typhimurium (strains TA1535, TA100, TA1537, TA1538, TA98) were used to evaluate the genotoxicity of cocoa and two of its constituents: theobromine (ThB) and caffeine (CA). Not roasted cocoa administered by stomach tube at doses of 0.1-0.6 g/animal caused a dose-dependent elevation of bone-marrow SCEs; roasted cocoa (chocolate liquor) gave almost identical results. Extraction of the fat (47% of cocoa) almost doubled the number of SCEs at the highest cocoa dose, to 10.01/cell, and increased the number of SCEs at all other doses somewhat less (range 5.33-7.88 SCEs/cell). Cocoa butter and ThB- and fat-free cocoa caused no significant elevation of SCEs. ThB alone at doses of 2.5-20 mg/animal, and ThB + CA (6:1) at the same doses caused similar high levels of SCEs (4.77-9.50) in a dose-dependent way. The micronucleus test was negative for roasted and fat-free cocoa, 0.6 g/animal, but highly positive for ThB (doses 2 x 20, 30, or 40 mg ThB), but ThB (dose 1 x 20, 30, or 40 mg/animal) gave negative results in the chromosome aberration test. None of the Salmonella strains showed any mutagenic effect of cocoa at concentrations of 5.0, 2.5, 1.0, and 0.5%; greater than or equal to 5.0% cocoa was antibacterial. ThB at 0.25% gave no evidence of mutagenicity with or without metabolic activation. ThB is evidently not demethylated in all mammals, and hence its non-mutagenicity cannot be assumed. (16 Refs)

52. EXAMINATION OF CHILI PEPPER AND NUTMEG OLEORESINS USING THE SALMONELLA/MAMMALIAN MICROSOME MUTAGENICITY ASSAY.

Buchanan RL, Goldstein S, Budroe JD
Dept. Nutrition and Food Sciences, Drexel Univ., Philadelphia, PA, 19104
J Food Sci; 47(1):330-331,333 1982

Past investigations have suggested that various arylalkene spice compounds warrant further study as possible naturally occurring mutagens and/or carcinogens. The present study carried out a detailed examination of nutmeg oleoresin, myristicin, chili pepper oleoresin, capsaicin, and vanillylamine for in vitro mutagenicity using the Salmonella/mammalian microsome mutagenicity assay. None of the materials tested displayed significant mutagenicity over a wide range of concentrations. (Author abstract) (43 Refs)

53. MUTAGENICITY OF GAMMA-IRRADIATED OXYGENATED AND DEOXYGENATED SOLUTIONS OF 2-DEOXY-D-RIBOSE AND D-RIBOSE IN SALMONELLA TYPHIMURIUM.

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Mutat Res; 90(4):385-397 1981

Mutagenic activity (MA) of soln of 2-deoxy-D-ribose (2DDR) and D-ribose (DR) irradiated under different conditions was studied in Salmonella typhimurium strains TA98, TA100, TA1535, TA1537, and TA1538. Metabolic activation was provided by S9 mix prepared from liver homogenates from Wistar rats treated with Aroclor. Test soln were irradiated with gamma-radiation (0.12-0.14 kilogray(kGy)/min; total dose 10 kGy). Before and during irradiation highly purified O_2, N_2, or N_2O was bubbled through the soln. H_2O_2 present in irradiated oxygenated soln showed MA in TA98 and TA1537. MA of H_2O_2 was eliminated in the presence of S9. Irradiated soln of 2DDR or DR were mutagenic in TA98 and TA100 but not in the other strains. In the absence of S9, N_2O-saturated soln of 2DDR showed greater MA than N_2-saturated soln, suggesting that the OH radical is involved in production of mutagenic products of radiolysis. Malonaldehyde (MDA) was not mutagenic at concentrations produced by irradiation. MA of individual products of radiolysis were not determined. MA of irradiated 2DDR soln in TA100 increased with the level of aldehydes other than MDA. MA of irradiated 2DDR soln was reduced in a temperature-dependent manner by heating of the soln, supporting the hypothesis that MA is caused by carbonyl or dicarbonyl compounds. Autoclaved, nonirradiated soln of 2DDR showed no MA in S typhimurium. (22 Refs)

54. STUDIES TO EVALUATE ARTIFICIAL SWEETENERS, ESPECIALLY REMSEN-FAHLBERG SACCHARIN, AND THEIR POSSIBLE IMPURITIES, FOR POTENTIAL MUTAGENICITY BY THE SALMONELLA/MAMMALIAN LIVER MICROSOME TEST.

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Mutat Res; 90(4):365-372 1981

Mutagenic activity (MA) of artificial sweeteners and some possible impurities of artificial sweeteners was studied in Salmonella typhimurium with or without metabolic activation by S9. S9 was prepared from livers of Sprague-Dawley rats. Bacterial cultures were exposed to saccharin (Sacc: less than or equal to 12,500 ug/plate), o-toluene sulfonamide or p-toluene sulfonamide (less than or equal to 18,000 ug/plate), o-sulfamoylbenzoic acid, p-sulfamoylbenzoic acid, o-sulfobenzoic acid, p-sulfobenzoic acid, phthalimide, anthranilic acid, disulfide salt, boiled saccharin, or one of three saccharin extracts (all less than or equal to 2,500 ug/plate), cyclamate (less than or equal to 12,500 ug/plate), or cyclohexylamine (less than or equal to 2,500 ug/plate). Cyclophosphamide (less than or equal to 100 ug/plate) and trypaflavine (less than or equal to 200 ug/plate) were used as positive controls. All Sacc tested was prepared by the Remsen-Fahlberg process. With the exception of one Sacc extract, all chemicals tested were negative for MA in the standard Ames assay. One organic extract of Sacc produced inconclusive results in three consecutive experiments. Results indicate that neither Sacc, cyclamate, cyclohexylamine, nor known impurities of the sweeteners are mutagenic in the Salmonella/mammalian liver microsome test. (23 Refs)

55. ABSENCE OF MUTAGENIC AND CLASTOGENIC ACTION OF PINE-TAR RESIN IN THE SALMONELLA/MICROSOMAL AND CHO CULTURE SYSTEMS.

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Mutat Res; 103(3-6):229-232 1982

Salmonella typhimurium strains TA98 and TA100, with and without S9 mix prepared from livers of rats pretreated with Aroclor 1254, were subjected to doses of 0.1-4 mg/plate of the natural pine tar resin used in Greek 'retsina' wine in the Ames test. Sister-chromatid exchanges, chromatid abnormalities, and mitotic index were determined for Chinese hamster ovary cells (CHO) subjected to doses of 0.025-1 mg/ml of the same resin. Neither test indicated mutagenicity, but mitotic arrest of CHO cells was evident at all concentrations tested. (10 Refs)

56. CHARACTERIZATION, BIOLOGIC ACTIVITY AND MUTAGENICITY OF PROTEIN FROM CIGARETTE TOBACCO, SMOKE AND PIPE CONDENSATE (MEETING ABSTRACT).

Misconi LY, Steward AM
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Clinical Oncology Society of Australia, November 24-17, 1981, Melbourne, Australia. The Society 70 pp., 1981.

The proteins of several extracts of tobacco, smoke and smoke condensate, were examined by mol wt, isoelectric point, (pI), presence of subunits, mutation and immunogenecity. Total protein levels were determined by the Lowry method. The non-protein components were removed by dialysis and ultra-filtration. Hplc, (High pressure liquid chromatography), using TSK3000 SW column (Beckman), resolved high and low mol wt proteins. The solvent system used was 0.2M Na_2SO_4, 0.01M $Na\text{-}PO_4$ buffer pH 6.5, the flow rate was 0.5-1.0 ml/min. The linear relationship between elution vol and mol wt of standard globular proteins allowed determination of mol wt. Up to 12 different proteins were identified by SDS-PAGE (sodium dodecyl sulfate - polyacrylamide gel electrophoresis and mercaptoethanol, which ranged between 20,000-150,000 daltons. This separation had the advantages of mol wt determination and the possible fractionation of the highest mol wt protein into its smaller subunits. When the highest mol wt band (150,000) was reapplied to a fresh SDS-PAGE, two bands were obtained of MW 150,000 and 85,000: when the latter band alone was applied to SDS-PAGE, both hands again appeared, suggesting the existence of aggregates. Dh skin activity was confined to these larger MW bands. Isoelectric focusing was performed using LKB Ampholine pH 3-11 PAGE gels. The focusing pattern demonstrated pI values (4.3-5.8) and the ampholyte mixture exhibited a linear pH profile. The Salmonella/mammalian-microsome mutagenicity test (Ames Assay-TA98 and TA100) wit h and without metabolic activation was applied to protein fractions obtained from tobacco, smoke and pipe smoke condensate, and significant mutagenic activity was detected. (no Refs)

57. INVESTIGATION OF MAILLARD PRODUCTS IN BACTERIAL MUTAGENICITY TEST SYSTEMS.

Aeschbacher HU, Chappuis C, Manganel M, Aeschbach R
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Prog Food Nutr Sci; 5(1-6):279-293 1981

In view of the recent interest in possible cancer risk from heated foods, the Ames test for mutagenicity was performed on certain heated foods. The plate mutagenicity test using Salmonella tester strains TA 1535, 1537, 1538, 98 and 100 was employed with and without metabolic activation. Food caramel, obtained from heating pure sugar, was not mutagenic. A liquid preparation was tested as was a powder and its three fractions. A plant protein hydrolysate (Maggie seasoning) also was found to be nonmutagenic. A heated mixture of arginine-glucose induced a slight mutagenic effect in Salmonella TA 100 (base pair substitution) but not in TA 98. The effect was abolished when the microsomal fraction (S-9 mix) was present together with the arginine-glucose. The pure compounds 2,5 dimethyl pyrazine and hydroxy-methylfurfural were negative in the Ames test. (11 Refs)

58. COMPARISON OF THE FREQUENCIES OF SCES INDUCED BY CHEMICAL MUTAGENS IN BONE-MARROW, SPLEEN AND SPERMATOGONIAL CELLS OF MICE.

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Mutat Res; 103(2):191-195 1982

Dose-effect curves are described for the incidence of sister chromatid exchanges (SCE) in Swiss mouse bone marrow, spleen, and spermatogonial cells previously treated in vivo with chemical mutagens (methyl methanesulfonate [MMS]; mitomycin C [MMC]; cyclophosphamide [CP]; 4-nitroquinoline oxide, [4NQO]; bleomycin [BLE]) to evaluate the relative sensitivity of the cell types to SCE-induction by each mutagen. Spontaneous SCE levels were the same for the three cell types, and SCE levels induced by mutagens were similar in the bone marrow and spleen cells, but were significantly less in spermatogonial cells. Mutagen effects on SCE were concentration-dependent, but not linear, suggesting detoxification by the cells at lower doses, even with MMS, which does not require metabolic activation. CP and MMC were efficient mutagens but 4NQO and BLE were not. Spermatogonial cells were evidently better protected against mutagens than the other cells. The SCE method should allow reliable comparison of mutagen sensitivities between somatic and germinal tissues. (17 Refs)

59. LIVER-MICROSOME S9 ENZYME INCREASES SPONTANEOUS BACKGROUND MUTATION FREQUENCY IN THE AMES SALMONELLA TEST SYSTEM IN THE ABSENCE OF ANY ADDED MUTAGEN.

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Div. Biological and Medical Res., Argonne Natl. Lab., Argonne, IL, 60439
Mutat Res; 103(3-6):263-265 1982

The number of spontaneous reversions of Salmonella typhimurium TA98 to prototrophy was measured 290 times, including 231 assays with 20, 50, and 50 ul/plate of Aroclor 1254-induced rat-liver S9 preparation. Numbers of spontaneous revertants in S9-treated plates were about 30% above the control for all three concentrations, and the differences were highly significant. Possible mechanisms suggested include S9 activation of some component in the plating medium or the presence of a nutrient in the S9. (3 Refs)

60. MICROSOME-MEDIATED CYTOTOXICITY TO CHO CELLS.

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Univ. Tennessee-Oak Ridge Graduate Sch. Biomedical Sciences, Oak Ridge, TN, 37830
Mutat Res; 103(3-6):359-365 1982

Purified microsomes from Aroclor 1254-induced liver S9 from Sprague-Dawley rats were used to prepare a microsomal activation system. With added NADP [0.01-4.00 milli (m) M] the microsomal activator was toxic to the Chinese hamster ovary cells used, unless Ca++ was present or glucose-6-phosphate was absent, suggesting that NADPH-catalyzed microsomal lipid peroxidation might be involved. Addition of 4 mM CaC12 or 2 uM butylated hydroxyanisole (antioxidant) inhibited the microsome-mediated cytotoxicity. Cytotoxicity of microsomes increased over the range 0-150 ul/ml of activation system, but mutation frequency at the hypoxanthine-guanine phosphoribosyl transferase locus was nil at all concentrations. (14 Refs)

BINDING OF CARCINOGENS AND THEIR METABOLITES TO MACROMOLECULES

61. FORMATION AND REMOVAL OF 7,12-DIMETHYLBENZ[A]ANTHRACENE-NUCLEIC ACID ADDUCTS IN RAT MAMMARY EPITHELIAL CELLS WITH DIFFERENT SUSCEPTIBILITY TO CARCINOGENESIS.

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Carcinogenesis; 2(12):1327-1333 1981

The susceptibility of the rat mammary gland to 7,12-dimethylbenz[a]anthracene (DMBA)-induced carcinogenesis is max when DMBA is fed to young virgin rats, diminishing with increasing age and becoming almost nil when pregnancy and lactation occur prior to carcinogen administration. This present study was carried out to determine whether these differences in susceptibility to DMBA are related to the ability of the gland to form and/or remove DMBA-nucleic acid adducts. Primary mammary epithelial cell cultures derived from young virgin (YV), old virgin (OV) and parous (P) Sprague-Dawley rats were treated in vitro with [3H]-DMBA for 24 hr. Hydrolysates of DNA isolated from these cells were chromatographed on Sephadex L H-20 columns. In cells from the three groups of animals, the chromatographic profiles were qualitatively similar with three 3H-labeled products eluting in the region expected for hydrocarbon-nucleoside adducts. This similarity in profiles suggested that identical DMBA-nucleic acid adducts are generated in each group. The chromatographic data are also consistent with the hypothesis that the hydrocarbon-DNA adducts of DMBA were generated through reactions of a 'bay-region' diol-epoxide of DMBA with DNA. Excision of DMBA-DNA adducts was investigated by measuring the time-dependent decrease in specific activity of the less dense parental DNA peak following centrifugation on alkaline CsCl gradients. Within 48 hr post-DMBA treatment, P cells removed approx 36% of the adducts from DNA with YV and OV cells removed only 24% and 12% of the adducts respectively. In addition, P cells excised the adducts at a rate 1.5 and 5x faster than either YV or OV cells. These results suggest that the lower susceptibility of the parous rat towards DMBA-induced carcinogenesis may be due not to the generation of different DMBA-DNA adducts, but to a more efficient DNA repair mechanism that is the result of increased gland differentiation through the process of pregnancy and lactation. (Author abstract) (56 Refs)

62. THE METABOLIC ACTIVATION OF DIBENZ[A,C]ANTHRACENE.

Hewer A, Cooper CS, Ribeiro O, Pal K, Grover PL, Sims P
Chester Beatty Res. Inst., Inst. Cancer Res., Royal Cancer Hosp., Fulham Road, London SW3 6JB, England
Carcinogenesis; 2(12):1345-1352 1981

In rat liver microsomal preparations, the 10,11-dihydrodiol of dibenz[a,c]anthracene (DBA) is metabolized to r-10,t-11-dihydroxy-t-12,13-oxy-10,11,12,13 tetrahydrodibenz[a,c]anthracene (anti-DBA 10,11-diol 12,13-oxide), the anti isomer of a non-bay-region diol-epoxide of DBA. When 3H-labelled DBA or trans-10,11-dihydroxydibenz[a,c]anthracene were metabolized in this system in the presence of DNA or when 3H-labelled DBA was added to primary cultures of hamster embryo cells, covalent reactions of hydrocarbon metabolites with DNA occurred.

The chromatographic characteristics of the radioactive hydrocarbon-deoxyribonucleoside adducts formed in these reactions were examined using Sephadex LH20 column chromatography and high pressure liquid chromatography. The results showed that whilst some of the radioactive hydrocarbon-deoxyribonucleoside adducts formed were indistinguishable from adducts that were formed when anti-DBA 10,11-diol 12,13-oxide reacted with DNA, other, unidentified adducts, which did not apparently rise from reactions of this diol-epoxide with DNA, were also present. Hydrocarbon-nucleoside adducts were not detected in hydrolysates of nucleic acids that were isolated from mouse skin that had been treated in vivo with DBA. (Author abstract) (30 Refs)

63. RELATIONSHIPS BETWEEN MICROSOMAL METABOLISM, DNA DAMAGE AND ADDUCT BINDING IN POLYCYCLIC HYDROCARBON-EXPOSED LUNG (MEETING ABSTRACT).

Haski R, Stewart BW
Department of Pathology, University of New South Wales, Kensington, Australia
Clinical Oncology Society of Australia, November 24-17, 1981, Melbourne, Australia. The Society 70 pp., 1981.

Preparations of isolated lung DNA from rats treated by intra-tracheal instillation of 3-methylcholanthrene (3MC) may be distinguished from control preparations by the extent of structural damage to the nucleic acid. In the study to be described, damage to DNA was determined by benzoylated-diethylaminoethyl cellulose chromatography. To analyze the relationship between metabolism of 3MC and subsequent DNA damage, the effect of modifiers of cytochrome P-450 (P-450) on both parameters was examined. Initially, measurement was made of P-450 content of rat lung at various times after administration of the hydrocarbon. In this manner experimental conditions for the use of an inducing dose of 3MC were determined and criteria were available to examine the efficacy of carbon tetrachloride-inhalation as a means of inhibiting 3MC metabolism. Animals were then treated either with an inducing dose of 3MC or by prior exposure to carbon tetrachloride to perturb microsomal metabolism of the carcinogen. The subsequent effect, on 3MC-induced DNA damage and repair, was determined. In addition, the covalent binding of 3MC to lung DNA was assayed using LH-20 chromatography. The findings indicate that the extent of polycyclic hydrocarbon-induced DNA damage in lung may be subject to wide variation as a consequence of exposure to agents which modifiy the rate of carcinogen metabolism. (no Refs)

64. FREE RADICAL METABOLISM OF MUTAGENIC ACRIDINES AND BINDING TO MICROSOMAL MEMBRANES.

Sinha BK
Lab. Environmental Biophysics, National Inst. Environmental Health Sciences, Res. Triangle Park, NC, 27709
Biochem Biophys Res Commun; 103(4):1166-1171 1981

Free radical metabolism of the acridine derivatives quinacrine and 9-aminoacridine was studied using horseradish peroxidase-H_2O_2 and prostaglandin-arachidonic acid systems. Incubation of the acridines resulted in NADPH-dependent covalent binding to microsomal membranes, although no radical could be detected. Free radical metabolism and covalent binding may play a significant role in the mutagenic properties of quinacrine and 9-aminoacridine. (13 Refs)

65. ALKYLATION OF DNA AND TISSUE SPECIFICITY IN NITROSAMINE CARCINOGENESIS.

Montesano R
International Agency for Res. on Cancer, 150, Cours Albert Thomas, 69372 Lyon Cedex 2, France
J Supramol Struct Cell Biochem; 17(3):259-273 1981

Evidence that the initiation of the carcinogenic process by nitrosamines is linked to the metabolic competence of the target tissue or cell to convert carcinogens into mutagenic metabolites, and to the binding of those metabolites to cellular DNA is reviewed. Alkylation of DNA occurs at the N-1, N-3, and N-7 positions of adenine; N-3, N-7, and O6 of guanine; N-3 and O2 of cytosine; N-3, O4, and O2 of thymine; and the phosphate groups. The initial proportion of each DNA adduct depends upon the alkylating agent. Alkylation at the oxygen atoms of DNA bases is more critical than alkylation at other positions in the mutagenesis and carcinogenesis induced by N-nitroso compounds. Tissues in which tumors occur more frequently are those in which O6-alkylguanine persists longest in DNA. The more rapid removal of O6-methylguanine from DNA of rat liver is associated with the absence of tumor production in this organ by a single dose of dimethylnitrosamine (DMN). Significant incidence of liver tumors is observed if the same dose is given 24 hr after partial hepatectomy. Data indicate that the rate of disappearance of 7-methylguanine from the liver or extrahepatic tissues is independent of DMN dose; O6-methylguanine is lost from DNA more rapidly after a low dose of DMN. The removal of O6-methylguanine from DNA can be affected by pretreating the animals with N-nitroso compounds. The modulation of DNA repair processes is discussed in relation to the tissue-specific carcinogenic effect of N-nitroso compounds. (132 Refs)

66. STUDY OF TARGET CELLS FOR ANTINEOPLASTIC AGENT METHYLNITROSOUREA.

Sharf VG, Pulatova MK, Emanuel' NM
Inst. Chemical Physics, Moscow, USSR
Dokl Akad Nauk SSSR; 261(4):1001-1005 1981

Characteristic features of methylnitrosourea (MNU) metabolism were studied in homogenates of mouse liver. Analysis of the electron paramagnetic resonance spectra showed the formation of the nitrosyl complexes of heme proteins. These findings indicated that Hb and cytochromes are the molecular targets for reduced MNU. (6 Refs) (In RUS)

67. DNA-DAMAGING ACTIVITY IN VIVO AND BACTERIAL MUTAGENICITY OF SIXTEEN AROMATIC AMINES AND AZO-DERIVATIVES, AS RELATED QUANTITATIVELY TO THEIR CARCINOGENICITY.

Parodi S, Taningher M, Russo P, Pala M, Tamaro M, Monti-Bragadin C
Dept. Oncology, Genoa Univ., Genoa, Italy
Carcinogenesis; 2(12):1317-1326 1981

Sixteen aromatic amines and azo-derivatives were studied. They were: benzidine; 2-acetylaminofluorene; 3'-methyl-p-dimethylaminobenzene; o-aminoazo-toluene; p-dimethylaminoazobenzene; 2,4-diaminotoluene; 4,4'-oxydianiline; 2,4-diaminoanisole; 4,4'-methylenedianiline; 2-naphthylamine; Auramine O; Rhodamine B; Ponceau MX; 1-naphthylamine; p-aminoazobenzene and aniline. The compounds were examined for their capability to induce alkaline DNA fragmentation in rat liver after treatment in vivo, for their mutagenicity in the Salmonella strains TA 98 and TA 100, for their acute toxicity and for their carc inogenicity in mice and rats. For each parameter a quantitative potency index was established, and the correlation existing amongst the different parameters investigated. Only mutagenicity in the strain TA 98 was slightly correlated with carcinogenic potency (r = 0.408). DNA fragmentation and toxicity were not correlated with carcinogenicity. A significant correlation was found between DNA fragmentation and toxicity (r = 0.539). No correlation was found between DNA fragmentation and mutagenicity. The lack of correlation between DNA fragmentation and carcinogenicity is in contrast with previous results obtained with a family of hydrazine derivatives and a group of nitroso compounds. For these two groups of chemicals correlation between DNA fragmentation and carcinogenicity existed, but not between carcinogenicity and mutagenicity in the Ames' test. It is suggested that short term tests can perform very differently for different classes of chemicals. (Author abstract) (22 Refs)

68. PHOTOCHEMICAL EPOXIDATION OF AFLATOXIN B1 AND STERIGMATOCYSTIN: SYNTHESIS OF GUANINE-CONTAINING ADDUCTS.

Buchi G, Fowler KW, Nadzan AM
Dept. Chemistry, Massachusetts Inst. Technology, Cambridge, MA, 02139
J Am Chem Soc; 104(2):544-547 1982

Benzil-sensitized photoepoxidation of the mycotoxins aflatoxin B1 and sterigmatocystin provided the presumed reactive epoxides which have been implicated in mutagenesis and carcinogenesis. These intermediates, after trapping with 3',5'-di-O-butyryldeoxyguanosine and hydrolysis with aqueous acid, led to the N(7)-guanine adducts identical with the in vivo natural products. This method provides an alternative to the more complex procedures of organ perfusion and whole body dosing. (Author abstract) (26 Refs)

ALTERATION OF MIXED FUNCTION OXIDASES BY CARCINOGENS

69. MIXED-FUNCTION AMINE OXIDASE OF THE RAT HEPATOCYTE NUCLEAR ENVELOPE. DEMONSTRATION AND EFFECTS OF PHENOBARBITAL AND 3-METHYLCHOLANTHRENE.

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American Critical Care, 1600 Waukegan Road, McGaw Park, IL, 60085
Biochem Pharmacol; 31(1):69-73 1982

Mixed-function amine oxidase has been demonstrated in highly purified rat hepatocyte nuclear envelope. The enzyme was present in the nuclear envelope at a level 20% of that observed in microsomes. Induction studies indicated that nuclear envelope amine oxidase as well as its microsomal counterpart were refractory to the effects of phenobarbital and 3-methylcholanthrene. Phenobarbital administration increased the specific activity of the microsomal N,N-dimethylaniline N-demethylase and benzo[a]pyrene hydroxylase by 600 and 190%, respectively, but decreased the specific activity of the nuclear enzymes by 30-50%. In contrast, 3-methylcholanthrene increased the specific activity of benzo[a]pyrene hydroxylase in nuclear envelope and microsomes by 42-and 11-fold, respectively. The hydrocarbon also increased the microsomal and nuclear N,N-dimethylaniline N-demethylase by 40 and 60%, respectively, but the specific activity of microsomal and nuclear aniline 4-hydroxylase was decreased by 50%. Demonstration of amine oxidase in rat hepatocyte nuclear envelope implicates this enzyme in the toxicity and carcinogenicity of certain drugs and chemicals. (Author abstract) (71 Refs)

70. THE AH REGULATORY GENE PRODUCT, SURVEY OF NINETEEN POLYCYLIC AROMATIC COMPOUNDS' AND FIFTEEN BENZO(A)PYRENE METABOLITES' CAPACITY TO BIND TO THE CYTOSOLIC RECEPTOR.

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Developmental Pharmacology Branch, Natl. Inst. Child Health and Human Development, NIH, Bethesda, MD, 20205
Toxicol Lett; 10(1):109-118 1982

The capacity of 19 polycyclic aromatic compounds and 15 benzo(a)pyrene metabolites to displace [1,6-3H]-2,3,7,8-tetrachlorodibenzo-p-dioxine (3HTCDD) from a hepatic cytosol Ah receptor from C57BL/6N mice was measured by scintillation spectrometry, after removal of the unbound TCDD by dextran-coated charcoal and sucrose density gradient centrifugation of the remaining sample. TCDD, dibenzo(a,h)anthracene, dibenzo(a,c)anthracene, benzo(a)pyrene, and 3-methylcholanthrene were the most effective in displacement of 3HTCDD from the Ah receptor. There was good agreement between these results and previously published studies on induction of monooxygenase activities. The capacity of Hepa-1 cells to metabolize polycyclic aromatic compounds was approx (lowest to highest): TCDD less than benzo(e)pyrene less than benzo(a)anthracene less than 3-methylcholanthrene approx = dibenzo(a,h)anthracene, which has no relationship to the rankings of these compounds as displacers of 3HTCDD. For all 15 benzo(a)pyrene metabolites examined, these was generally a correlation between percent displacement of 3HTCDD from the Ah receptor and fold induction of aryl hydrocarbon hydroxylase (AHH) activity. For all the compounds tested there is a good correlation between the displacement of 3HTCDD from the Ah receptor and the capacity to induce AHH activity, azo dye N-demethylase activity, or zoxazolamine metabolism. (36 Refs)

71. 1,1,1-TRICHLOROPROPENE-2,3-OXIDE: AN ALTERNATE MECHANISM FOR ITS INHIBITION OF CYTOCHROME P-450.

Ivanetich KM, Ziman MR, Bradshaw JJ
Dept. Medical Biochemistry, Univ. Cape Town Medical Sch., Observatory, Cape Province, 7925, South Africa
Res Commun Chem Pathol Pharmacol; 35(1):111-120 1982

Incubation of hepatic microsomes from phenobarbital treated rats, 1,1,1-trichloropropene-2,3-oxide (TCPO; 3 mM), EDTA (0.2 mM) and NADPH-generating system in vitro decreased the levels of cytochrome P-450 by 40% and equivalently decreased microsomal heme. Appreciable losses of cytochrome P-450 were not observed [1] if metyrapone (2.3 mM) or CO:O2 (80:20; v/v) were included in incubation mixtures, [2] if the TCPO or NADPH-generating system were omitted from reaction mixtures, or [3] if microsomes from untreated or beta-naphthoflavone treated rats were utilized. The time course for the TCPO mediated loss of hepatic microsomal cytochrome P-450 showed a time lag of 5 min, before the levels of cytochrome P-450 were significantly altered, followed by a 10-15 min period in which the levels of cytochrome P-450 rapidly decreased to a non-zero plateau level. The concentration of TCPO required for half maximal loss of cytochrome P-450 was ca 0.5 mM. In the absence of cytochrome P-450 degradation, TCPO (2 mM) was an effective inhibitor of aminopyrene demethylase and benzpyrene-3-hydroxylase but not of p-nitroanisole demethylase or ethoxyresofurin deethylase. In contrast, the degradation of cytochrome P-450 by TCPO strikingly decreased ethoxyresofurin deethylase and to a lesser extent p-nitroanisole demethylase. A reaction mechanism is proposed for the TCPO mediated degradation of cytochrome P-450 in vitro. (Author abstract) (21 Refs)

72. INDUCTION OF DRUG-METABOLIZING ENZYMES IN THE RAT LIVER BY 3'-METHYL-4-(DIMETHYLAMINO)AZOBENZENE.

Hino O, Nemoto N, Nagao M, Kosugi A, Kitagawa T
Dept. Pathology, Cancer Inst., Kami-Ikebukuro 1-37-1, Toshima-ku, Tokyo 170, Japan
Cancer Lett; 15(2):131-136 1982

The hepatic drug metabolizing system was examined in male Donryu rats fed a normal diet or a diet containing 3'-methyl-4-(dimethylamino)azobenzene (3'-Me-DAB: 1-600 ppm) for 1 or 3 wk. Microsomal cytochrome P-450 content was not affected after 1 wk of 3'-Me-DAB administration but was significantly higher after 3 wk of treatment with 10, 20, or 600 ppm of the carcinogen. Liver S-9 fraction from rats treated with 3'-Me-DAB (20 or 300 ppm, 3 wk) produced a significant, dose-dependent increase in number of 3-methylcholanthrene-induced revertants in the Ames test; when 3-amino-1-methyl-5H-pyrido[4,3-b]indole was used as the mutagen, a significant increase in the number of revertants was induced by S-9 from rats treated with the higher dose. The results indicate that dietary 3'-Me-DAB induces cytochrome P-450 in the liver and that the increase in drug metabolizing capacity can be detected efficiently by the Ames Salmonella test. (25 Refs)

73. INDUCTION OF CYTOCHROME P-450 RELATED METABOLIC ACTIVITIES IN THE RAT VENTRAL PROSTATE.

Soderkvist P, Toftgard R, Gustafsson JA
Dept. Pharmacology, Karolinska Inst., Box 60 400, S-104 01 Stockholm, Sweden
Toxicol Lett; 10(1):61-69 1982

Male Sprague-Dawley rats were received ip 80 mg/kg beta-naphthoflavone (BNF) or phenobarbital (PB) each day for 4 days. BNF treatment increased the ventral prostatic microsomal cytochrome P-450 content from 0.002 to 0.056 nanomole/mg protein and caused the diathionite-reduced minus oxidized difference spectrum peak to shift from 450 tp 448 nanometers. BNF treatment increased 7-ethoxyresorufin-O-deethylase (7-EOD) activity 800-fold and aryl hydrocarbon hydroxylase (AHH) activity 1000-fold; PB had no significant effects. Neither treatment increased NADPH-cytochrome c reductase activity. Activities of the same three enzymes in liver microsomes were elevated by BNF relatively less than in prostatic microsomes. The major metabolic products found after incubation of microsomes with BP were phenols. Both dihydrodiols and phenols were found in increased amounts after BNF treatment; the effect was more pronounced in liver microsomes than in prostatic microsomes. Activity of 7-EOD in prostatic microsomes was abolished in microsomes from both control and BNF-treated rats when samples were assayed without NADPH, gassed with CO for 60 sec, or treated with 70 uM alpha-naphthoflavone (ANF); 7 uM ANF completely inhibited activity in the controls and caused 98% inhibition of 7-EOD in microsomes of BNF-treated rats. ANF concentrations of 7 and 70 uM caused 42% and 78% decreases in AHH activity in prostatic microsomes of BNF-treated rats. NADPH-deficiency totally abolished AHH activity. The inhibition of enzymatic activity by known inhibitors of cytochrome P-450 indicate that these activities in rat prostatic microsomes are cytochrome P-450-mediated reactions. (27 Refs)

74. THE INDUCTION OF RAT LUNG ARYL HYDROCARBON HYDROXYLASE BY DILUTED SMOKE FROM COMMERCIAL CIGARETTES.

Bilimoria MH, Ecobichon DJ
Pathology Inst., McGill Univ., 3775 University St., Montreal, Quebec H3A 2B4, Canada
Toxicology; 22(3):205-210 1981

Induction of pulmonary aryl hydrocarbon hydroxylase (AHH) was studied by exposure of adult, male Sprague-Dawley rats to various dilutions of cigarette smoke for 200 sec. Three types of cigarettes were used for the study: plain-end cigarette which deliver 20 mg of tar (total particular matter [TPM], water and nicotine free) under standard smoking conditions and two low tar products, extra mild and ultra mild cigarettes, which deliver 4 mg and 1 mg tar, respectively. Rats exposed 1:5, 1:10 and 1;20 dilutions of smoke from plain-end cigarette showed a similar initial rate of induction of AHH, with significantly less effect with a 1:40 dilution. The smoke concentration in the exposure chamber contained approx 1.36 mg TPM/liter (l). Further dilution of smoke from plain-end cigarette was necessary to achieve clear dose-response relationships. When 40 puffs of a 1:5 dilution from the extra mild cigarette were drawn through the machine at a flow rate of 1.1 l/min, TPM concentration in the exposure chamber was 2.18 mg/l. Similar sampling of the ultra mild cigarette resulted in too little material being trapped to permit accurate weighing. Considerable AHH induction was observed at 1:40 dilution of the extra mild cigarette smoke. The extremely sensitive rat pulmonary enzyme system may prove valuable in the biological testing of modern low tar cigarettes. (18 Refs)

ALTERATION OF OTHER CARCINOGEN-METABOLIZING ENZYMES BY CARCINOGENS

75. THE EFFECTS OF BENZO(A)PYRENE ON RAT LIVER LYSOSOMES.

Carevic M, Carevic O
Res. Centre Medicine and Psychology Traffic, Sarengradska 3, 41000 Zagreb, Yugoslavia
Toxicol Lett; 10(1):41-49 1982

Male and female rats receiving ip injections of benzo(a)pyrene (BP, 10 mg/kg) showed increased release of hepatic beta-glucuronidase, beta-galactosidase, and beta-N-acetylglucosaminidase, followed by increased activities of these enzymes in blood plasma. Lysosome-enriched liver suspension incubated for 20 min at 37 C with increasing concentrations of BP (10(-7), 10(-6), and 10(-5) M) exhibited no significant changes in specific activities of these enzymes. BP, at the same three concentrations, caused increased release of the three enzymes during 20 min incubation in a concentration-dependent manner. Equal volume doses of dimethyl sulfoxide had no effect, or decreased release slightly. The observed lysosomal changes precede by several hours the onset of the altered cells or cell populations that appear in the liver approx 24 hr after BP administration. Injection of BP into rats may injure the lysolemma; injuries to the lysolemma may be an important feature of the early biochemical events in BP-initiated hepatocarcinogenesis. (29 Refs)

76. SEQUENTIAL CHANGES IN HISTOCHEMICAL LOCALIZATION OF EPOXIDE HYDROLASE AND GAMMA-GLUTAMYL TRANSPEPTIDASE DURING HEPATOCARCINOGENESIS (MEETING ABSTRACT).

Noda K, Fukumoto Y, Oki K, Takemoto T

1st Department Internal Medicine, Yamaguchi University School of Medicine, Ube, Japan

Proceedings of the Japanese Cancer Association, 40th Annual Meeting, October 1981, Sapporo, Japan. The Association 415 pp., 1981.

The subject of this study is the clarification of roles about microsomal epoxide hydrolase (EH) in promotion stage of chemical carcinogenesis. After diethylnitrosoamine (DEN) (200 mg/kg, ip), partial hepatectomy and 2-acetylaminofluorene (2-AAF) feeding (0.02%, 2 wk) were done. From 1 to 8 wk rats were sacrificed and liver tissues were fixed with ethanol. By means of peroxidase-antiperoxidase method, the changes of EH localization were studied, and also gamma glutamyl transferase (GGT) was examined by the consecutive liver tissue sections. From 2 wk the regression of EH was recognized in each focus. And in major parts of foci, GGT localized in those EH-negative areas as if in compensation. Furthermore, the change in a remodeling stage was studied with the intermittent 2-AAF feeding (0.05%) regimen. The different localization of the two kinds of marker enzymes is discussed. (no Refs)

77. INDUCTION OF RAT COLONIC EPITHELIAL ORNITHINE DECARBOXYLASE (ODC) BY BILE SALTS, AND ITS ENHANCEMENT BY COLON CARCINOGENS PRETREATMENT (MEETING ABSTRACT).

Takano S, Akagi M, Bryan GT

Department of Surgery, Kumamoto University, Kumamoto, Japan

Proceedings of the Japanese Cancer Association, 40th Annual Meeting, October 1981, Sapporo, Japan. The Association 415 pp., 1981.

A single intrarectal (ir) instillation of bile salts, presumptive colon promoters, results in a significant, early transient dose-response induction of rat colonic polyamine biosynthetic enzymes, ODC and S-adenosyl-L-methionine decarboxylase. Pretreatment by ir N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) or sc dimethylhydrazine (DMH) 1 wk before bile salt treatment enhanced and prolonged deoxycholate-induced ODC levels. This enhancement was dependent on pretreatment dose of MNNG, and was observed up to 3 mo after MNNG pretreatment. These data suggest that induced colonic ODC activity by bile salts may be related to colon carcinogenesis in a manner analogous to that shown to occur in mouse skin tumor systems. (no Refs)

78. REGULATION OF RAT ALPHA-FETOPROTEIN PRODUCTION BY METHIONINE DURING ETHIONINE-HEPATOCARCINOGENESIS.

Miyazaki M, Watanabe A
Div. Pathology, Cancer Inst., Okayama Univ., Okayama 700, Japan
Int J Cancer; 29(2):213-216 1982

The levels of serum alpha-fetoprotein (AFP) in rats were determined during hepatocarcinogenesis with ethionine, and the effects of methionine administration on serum AFP elevation in these animals were studied with the aim of investigating regulatory mechanisms of AFP production during carcinogenesis. Elevation of serum AFP was observed 6 wk following the start of feeding a diet containing 0.25% ethionine and again at the 22nd wk of feeding, when a well-differentiated hepatoma had already developed. These biphasic elevations of serum AFP concentrations in rats fed a 0.25% ethionine-containing diet decreased abruptly and significantly following a change to the basal diet either supplemented with or without 0.7% methionine. The possibility that regulation of AFP production in these rats may correlate with methionine metabolisms is discussed on the basis of the experimental data obtained. (Author abstract) (17 Refs)

REVIEWS AND OTHER RELEVANT STUDIES

79. THE PROBLEM OF METABOLISM OF DRUGS AND FOREIGN SUBSTANCES IN MAMMALIAN ORGANISMS.

Scheler W
Forschungszentrum fur Molekularbiologie und Medizin, AdW der DDR, Berlin, E. Germany
Sitzungsber Akad Wiss DDR; (21N):37-49 1981

Processes of drugs metabolism and other foreign substances in mammalian organisms are described. Metabolic processes convert inactive molecules to active ones, which then produce pharmacodynamic or toxic effects, depending on the molecule. Many of the effects of activated metabolites are reversible. Irreversible effects include mutagenic and carcinogenic effects. (no Refs) (In GER)

80. QUANTUM CHEMICAL STUDIES OF AFLATOXINS: METABOLISM AND CARCINOGENIC ACTIVITY.

Loew GH, Poulsen MT
SRI International, Life Sciences Div., Menlo Park, CA, 94025
Int J Quantum Chem Quantum Biol Symp; 8:95-107 1981

Semiempirical all-valence electron molecular orbital methods were used to further determine the extent to which the parent compound susceptibility to epoxidation and the stability of the epoxide and its carbocation play a role in determining the relative carcinogenic and mutagenic potencies of five aflatoxins (aflatoxin B1, aflatoxin G1, aflatoxin P1, aflatoxin M1, aflatoxicol) and two biosynthetic precursors (versacolorin A, sterigmatocystin). Results support the initial experimental findings that these electronic factors do not determine the relative potencies of aflatoxins or their biosynthetic precursors. (33 Refs)

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1. AN EVALUATION OF THE GENETIC TOXICITY OF EPICHLORHYDRIN. A REPORT OF AN EXPERT GROUP OF THE INTERNATIONAL COMMISSION FOR PROTECTION AGAINST ENVIRONMENTAL MUTAGENS AND CARCINOGENS.
Sram RJ, Tomatis L, Bridges BA, Clemmesen J
(c/o Lohman), Medical Biological Lab. TNO, P.O. Box 45, 2280 AA Rijswijk, The Netherlands
Mutat Res; 87(3):299-319 1981

2. ETHYLENE DIBROMIDE (EDB). (REVISED).
NIOSH Document Development Branch
Robert A. Taft Lab., National Inst. Occupational Safety and Health, 4676 Columbia Parkway, Cincinnati, OH, 45226
Curr Intell Bull NIOSH (37): 13 pp., 1981.

3. CHEMICAL CARCINOGENESIS AND SMOKING
Farber E
Dept. Pathology, Univ. Toronto, Banting Inst., 100 College St., Toronto, Ontario M5G 1L5, Canada
Can J Public Health; 72(6):381-385 1981

RADIATION CARCINOGENESIS

4. CELLULAR TRANSFORMATION BY RADIATION: INDUCTION, PROMOTION, AND INHIBITION.
Borek C
Radiological Res. Lab., Cancer Center/Inst. Cancer Res., Columbia Univ. Coll. Physicians and Surgeons, New York, NY, 10032
J Supramol Struct Cell Biochem; 16(4):311-336 1981

5. EFFECTS OF IONIZING RADIATION ON THE DEVELOPING EMBRYO AND FETUS: A REVIEW.
Hoffman DA, Felten RP, Cyr WH
Bureau Radiological Health, Rockville, MD
Effects of Ionizing Radiation on the Developing Embryo and Fetus: A Review. Available from National Technical Information Service, Springfield, VA, as PB82-115379, 160 pp., 1981.

DIETARY FACTORS IN CARCINOGENESIS

6. BETA-CARBOLINES, PSYCHOACTIVE COMPOUNDS IN THE MAMMALIAN BODY.
Airaksinen MM, Kari I
Dept. Pharmacology, Univ. Kuopio, P.O. Box 138, SF-70101 Kuopio 10, Finland
Med Biol; 59(4):190-201 1981

7. DIET AND CANCER OF THE LARGE BOWEL.
Zaridze DG
Analytical Epidemiology Programme, Div. Epidemiology and Biostatistics, International Agency for Res. on Cancer, 150 Cours Albert Thomas, 69372 Lyon, Cedex 2, France
Nutr Cancer; 2(4):241-249 1981

8. INFLUENCE OF DIET ON MAMMARY CANCER.
Carroll KK
Dept. Biochemistry, Univ. Western Ontario, London, Ontario, N6A 5C1, Canada
Nutr Cancer; 2(4):232-236 1981

9. ARTIFICIAL SWEETENERS IN RELATION TO THE EPIDEMIOLOGY OF BLADDER CANCER.
Howe GR, Burch JD
NCI Canada Epidemiology Unit, Univ. Toronto, Ontario, Canada
Nutr Cancer; 2(4):213-216 1981

EPIDEMIOLOGY, ETIOLOGY AND GENETIC ASPECTS OF HUMAN CANCER

10. EPIDEMIOLOGY AND THE STUDY OF CANCER.
Woods NF, Woods JS
Dept. Physiological Nursing, Sch. Nursing, Univ. Washington, Seattle, WA
Cancer Nursing. Marino LB, ed. St. Louis, The C. V. Mosby Company, 635 pp., 1981.

11. EPIDEMIOLOGY OF CUTANEOUS MALIGNANT MELANOMA.
Balda BR
Dermatologische Klinik und Poliklinik der Universitat, Frauenlobstr. 9-11, D-8000 Munchen 2, W. Germany
MMW; 123(50):1923-1926 1981
In GER

12. THE SMOKING-INDUCED EPIDEMIC.
Doll R
Green Coll. Oxford, Oxford, England
Can J Public Health; 72(6):372-381 1981

ENVIRONMENTAL AND OCCUPATIONAL FACTORS IN CARCINOGENESIS

13. HEALTH HAZARDS OF ASBESTOS EXPOSURE.
Kaw JL
Industrial Toxicology Res. Centre, Lucknow 226 001, India
J Sci Ind Res; 40(5):342-346 1981

14. OVERVIEW OF FINNISH EPIDEMIOLOGIC STUDIES ON OCCUPATIONAL CANCER.
Tola S
Dept. Epidemiology and Biometry, Inst. Occupational Health, Haartmaninkatu 1, SF-00290 Helsinki 29, Finland
Scand J Work Environ Health; 7(Suppl4):133-139 1981

CELLULAR AND MOLECULAR MECHANISMS IN CARCINOGENESIS

15. ALKYLATION OF DNA AND TISSUE SPECIFICITY IN NITROSAMINE CARCINOGENESIS.
Montesano R
International Agency for Res. on Cancer, 150, Cours Albert Thomas, 69372 Lyon Cedex 2, France
J Supramol Struct Cell Biochem; 17(3):259-273 1981

VIRAL AND IMMUNOLOGICAL ASPECTS OF CARCINOGENESIS

16. TRANSFORMATION INDUCED BY HERPES SIMPLEX VIRUS: A POTENTIALLY NOVEL TYPE OF VIRUS-CELL INTERACTION.
Hampar B
Lab. Molecular Virology, NCI, Frederick, MD, 21701
Adv Cancer Res; 35:27-47 1981

17. ONCOGENESIS BY RNA TUMOR VIRUSES.
Koyama T
Dept. Carcinostasis Res., Tokyo Univ. Medical Res. Inst. 4-6-1 Kindai, Minato-ku, Tokyo 138, Japan
Tanpakushitsu Kakusan Koso; 26(14):2121-2129 1981
In JPN

18. POLYOMA T ANTIGENS.
Eckhart W
Tumor Virology Lab., Salk Inst., San Diego, CA, 92138
Adv Cancer Res; 35:1-25 1981

METHODOLOGY IN CARCINOGENESIS RESEARCH

19. EPIDEMIOLOGICAL ASSESSMENT OF DIETARY INTAKE.
James WP, Bingham SA, Cole TJ
Medical Res. Council's Dunn Clinical Nutrition Center, Addenbrooke's Hosp., Cambridge, England
Nutr Cancer; 2(4):203-212 1981

20. ASSESSMENT OF TECHNOLOGIES FOR DETERMINING CANCER RISKS FROM THE ENVIRONMENT.
Office of Technology Assessment
Office of Technology Assessment, Washington, DC
Assessment of Technologies for Determining Cancer Risks from the Environment. Available from National Technical Information Service, Springfield, VA, as PB81-235400, 243 pp., 1981.

21. ANTIBODIES SPECIFIC FOR DNA COMPONENTS STRUCTURALLY MODIFIED BY CHEMICAL CARCINOGENS.
Muller R, Rajewsky MF
(c/o Rajewsky) Institut fur Zellbiologie (Tumorforschung), Universitat Essen (GH), Hufelandstrasse 55, Essen 1, W. Germany
J Cancer Res Clin Oncol; 102(2):99-113 1981

22. APPLICATION OF THE MICROBIAL MUTATION TEST IN OCCUPATIONAL HEALTH AND ITS FUTURE PROBLEMS.
Takemura N
Dept. Public Health, Jikei Univ., 25-8, Nishi-Shimbashi 2-chome, Minato-ku, Tokyo 105, Japan
Sangyo Igaku; 23(4):355-365 1981
In JPN

OTHER REVIEWS IN CARCINOGENESIS

23. ARACHIDONIC ACID TRANSFORMATION AND TUMOR PRODUCTION.
Levine L
Dept. Biochemistry, Brandeis Univ., Waltham, MA, 02254
Adv Cancer Res; 35:49-79 1981

24. POLYAMINES IN MAMMALIAN TUMORS PART I.
Scalabrino G, Ferioli ME
Inst. General Pathology, Univ. Milan, 20133 Milan, Italy
Adv Cancer Res; 35:151-268 1981

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MECHANISMS OF CARCINOGENESIS

Activation and Metabolism of Carcinogens

SERIES CK08 No. 82/07

JULY, 1982

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service • National Institutes of Health • National Cancer Institute

HE 20. 3173/2:

METABOLIC ACTIVATION OF CARCINOGENS

1. CARCINOGENICITY OF METHYLATED BENZO(A)PYRENE: CALCULATED EASE OF FORMATION OF THE BAY-REGION CARBONIUM ION.

Silverman BD
IBM Thomas J. Watson Res. Center, Yorktown Heights, NY, 10598
Cancer Biochem Biophys; 5(4):207-212 1981

The ease of carbonium ion formation in methylated benzo(a)pyrene (BP) was determined by calculating the difference in energy between diol-epoxide and triol-carbonium ion using two different molecular orbital programs. Substitution of a methyl group at either of the two positions adjacent to the benzo-ring, which becomes metabolized to the highly active diol-epoxide, induced changes that spanned the range of calculated reactivity. Substitution of a methyl group in the bay-region stabilized carbonium ion formation significantly. The order of differences in bay-region diol-epoxide and triol-carbonium ion energies for the monomethyl BPs corresponded closely to reported relative carcinogenicities for the compounds. (20 Refs)

2. AROMATIC HYDROCARBONS: METABOLISM BY BACTERIA, FUNGI AND ALGAE.

Cerniglia CE
Natl. Center for Toxicological Res., Food and Drug Admin., Jefferson, AR, 72079
Rev Biochem Toxicol; 3:321-361 1981

Microbial metabolism of aromatic hydrocarbons, including benzene, biphenyl, naphthalene, phenanthrene, anthracene, benzo(a)pyrene, and benz(a)anthracene, is reviewed. Enzymes involved in the microbial metabolism of aromatic hydrocarbons are described. The data demonstrates that bacteria, fungi, and algae have the enzymatic capacity to metabolize aromatic substrates that range in size from benzene to benzo(a)pyrene. It was also shown that fungi can metabolize polycyclic aromatic hydrocarbons to metabolites known to be carcinogenic, mutagenic, and acutely toxic to experimental animals. (153 Refs)

3. TUMOUR INITIATING ACTIVITY OF DIHYDRODIOLS OF BENZO[B]FLUORANTHENE, BENZO[J]FLUORANTHENE, AND BENZO[K]FLUORANTHENE.

LaVoie EJ, Amin S, Hecht SS, Furuya K, Hoffmann D
Naylor Dana Inst. Disease Prevention, Valhalla, NY, 10595
Carcinogenesis; 3(1):49-52 1982

The tumor initiating activities on mouse skin of benzo[b]fluoranthene, (B[b]F), benzo[j]fluoranthene (B[j]F), benzo[k]fluoranthene (B[k]F) and three of their dihydrodiols, 9,10-dihydro-9,10-dihydroxybenzo[b]fluoranthene (B[b]F-9,10-diol), 9,10-dihydro-9,10-dihydroxybenzo[j]fluoranthene (B[j]F-9,10-diol), and 8,9-dihydro-8,9-dihydroxybenzo[k]fluoranthene (B[k]F-8,9-diol) were evaluated. Among the parent hydrocarbons, B[b]F was the most potent tumor initiator, with activity greater than that of B[j]F but less than that of benzo[a]pyrene. B[k]F also showed tumor initiating activity, in contrast to its lack of complete carcinogenic activity on mouse skin. B[b]F-9,10-diol, which can form a bay region dihydrodiol epoxide, was as active as B[b]F. B[j]F-9,10-diol which would form its dihydrodiol epoxide in a four sided pseudo-bay region, was less active than B[j]F. B[j]F-8,9-diol was inactive. These results, together with parallel metabolic studies, suggest that the formation of bay region dihydrodiol epoxides may not be the major activation mechanism in benzofluoranthene tumorigenesis. (Author abstract) (25 Refs)

4. METABOLISM AND ACTIVATION OF AFLATOXIN B1 BY RECONSTITUTED CYTOCHROME P-450 SYST EM OF RAT LIVER.

Yoshizawa H, Uchimaru R, Kamataki T, Kato R, Ueno Y
(c/o Ueno) Dept. Toxicology and Microbial Chemistry, Science Univ. Tokyo, Ichigaya, Shinjuku-ku, Tokyo 162, Japan
Cancer Res; 42(3):1120-1124 1982

Metabolism and activation of aflatoxin B1, a potent hepatocarcinogenic and mutagenic mycotoxin of Aspergillus flavus, were investigated in the reconstituted enzyme system composed of purified NADPH-cytochrome P-450 reductase and cytochrome P-450 or P-448 or rat liver. The aflatoxin M1 formation was strictly mediated by P-448 purified from the liver microsomes of polychlorobiphenyl- and 3-methylcholanthrene-treated rats, while the aflatoxin Q1 formation, as well as the binding to DNA, were catalyzed by both P-450 and P-448. Differences between the kinetic data on metabolism and activation of aflatoxin B1 obtained with the reconstituted cytochrome systems and those obtained with the microsomal and nuclear systems were discussed, and the significance of these biochemical data in the in vivo carcinogenicity of aflatoxin B1 was evaluated. (Author abstract) (37 Refs)

5. ENDOGENOUS FORMATION OF N-NITROSO COMPOUNDS.

Tannenbaum SR, Goldman P, Goldin BR, Moore WE, Magee PN, Montesano R, Eisenbrand G
Dept. Nutrition and Food Science, Massachusetts Inst. Technology, Cambridge, MA, 02139
Banbury Rep; 7:269-273 1981

Although there is circumstantial evidence for the endogenous formation of N-nitroso compounds, the low reported levels of these substances in body fluids and tissues (ppb or less) raise serious questions about artefact formation and data interpretation. Experiments on the metabolism of N-dimethylnitrosamine (NDMA) led to the formulation of models which may or may not be accurate. A model of NDMA formation and clearance assumed a steady state between the two processes; the distribution of NDMA in total body water; first-order clearance from the blood; and approx equal rates of NDMA metabolism in rats and humans. In this model, the rate of NDMA clearance in a 70-kg man (total body water, 40 liters) is 0-0.7 ug/liter/hr, and the rate of NDMA formation is 0-10 ug/kg/day (max, 70 ug/day). The real values are probably between these extremes. Studies on urinary NDMA excretion in rats indicated a log/log relationship between the dose and the excreted quantity over 3 orders of magnitude. This model predicted that a blood concentration measured in ppb would be equivalent to a urinary concentration of parts per 10(11). If endogenous formation of N-nitroso compounds occurs in man, the risk would be at least additive to the risk provided by exogenous exposure. If endogenous formation of N-nitroso compounds does occur, it may be possible to limit that exposure by taking appropriate action. (2 Refs)

6. OXIDATIVE METABOLISM OF DIETHYLSTILBESTROL BY PROSTAGLANDIN SYNTHETASE.

Degen GH, Eling TE, McLachlan JA
(c/o McLachlan) Transplacental Toxicology Section,, Natl. Inst. Environmental Health Sciences, NIH, Research Triangle Park, NC, 27709
Cancer Res; 42(3):919-923 1982

The cooxidative metabolism of the transplacental carcinogen, diethylstilbestrol (DES), was examined using ram seminal vesicle microsomes. The major extractable metabolite was beta-dienestrol (Z,Z-DIES) and represented about 35% of the added DES in 3-min incubations supplemented with arachidonic acid. Its formation was dependent upon the presence of arachidonic acid, whereas reduced nicotinamide adenine dinucleotide phosphate failed to elicit Z,Z-DIES above background. Indomethacin and 1-phenyl-3-pyrazolidone, known inhibitors of prostaglandin synthetase, blocked Z,Z-DIES formation, probably by inhibiting the cyclooxygenase and the hydroperoxidase activities, respectively. Hydrogen peroxide and 15-hydroperoxyarachidonic acid (cosubstrates of the prostaglandin synthetase-hydroperoxidase), when replacing arachidonic acid in incubations, also supported oxidative metabolism of DES catalyzed by ram seminal vesicle microsomes. 1-Phenyl-3-pyrazolidone, but not indomethacin, inhibited the 15-hydroxyperoxy arachidonic acid-dependent formation of Z,Z-DIES. Incubation conditions which supported efficient Z,Z-DIES formation also resulted in the formation of 3,3-di(p-hydroxyphenyl)hexan-4-one and the cis-isomer of DES as well as nonextractable, protein-associated radioactivity indicating the presence of reactive intermediates. The implications of the peroxidative metabolism of DES for its toxic activity are obvious. (Author abstract) (40 Refs)

7. OXIDATION OF TRICHLOROETHYLENE BY LIVER MICROSOMAL CYTOCHROME P-450: EVIDENCE FOR CHLORINE MIGRATION IN A TRANSITION STATE NOT INVOLVING TRICHLOROETHYLENE OXIDE.

Miller RE, Guengerich FP
Dept. Pharmacology, Center Environmental Toxicology, Vanderbilt Univ. Sch. Medicine, Nashville, TN, 37232
Biochemistry; 21(5):1090-1097 1982

Trichloroethylene (TCE) was metabolized by cytochrome P-450 containing mixed-function oxidase systems to chloral (2,2,2-trichloroacetaldehyde), glyoxylic acid, formic acid, CO, and TCE oxide. TCE oxide was synthesized, and its breakdown products were analyzed. Under acidic aqueous conditions the primary products were glyoxylic acid and dichloroacetic acid. The primary compounds formed under neutral or basic aqueous conditions were formic acid and CO. TCE oxide did not form chloral in any of these or other aqueous systems, even when iron salts, ferriprotoporphyrin IX, or purified cytochrome P-450 was present. Ferric iron salts catalyzed the rearrangement of TCE oxide to chloral only in CH2Cl2 or CH3CN. A 500-fold excess of iron was required for complete conversion. A kinetic model involving the zero-order oxidation of TCE to TCE oxide by cytochrome P-450 and the first-order degradation of the epoxide was used to test the hypothesis that TCE oxide is an obligate intermediate in the conversion of TCE to other metabolites. kinetic constants for the breakdown to TCE oxide and for the oxidative metabolism of TCE to stable metabolites were used to predict epoxide concentrations required to support the obligate intermediacy of TCE oxide. The maximum levels of TCE oxide detected in systems using microsomal fractions and purified cytochrome P-450 were 5-28-fold lower than those predicted from the model. The kinetic data and the discrepancies between the observed metabolites and TCE oxide breakdown products support the view that the epoxide is not an obligate intermediate in the formation of chloral, and an alternative model is presented in which chlorine migration occurs in an oxygenated TCE-cytochrome P-450 transition state. (Author abstract) (29 Refs)

8. MICROSOMAL REDUCTION OF THE CARCINOGEN CHROMATE PRODUCES CHROMIUM(V).

Jeannette KW
Dept. Chemistry, Dartmouth Coll., Hanover, NH, 03755
J Am Chem Soc; 104(3):874-875 1982

Formation of a stable reactive intermediate upon metabolism of the inorganic carcinogen chromate by rat liver microsomes in the presence of NADPH is reported. A Cr(V) electrophrenic respiration signal is apparent within 20 sec at 22 C and is detectable for 80 min after initiation in the given conditions, indicating some stability. The stability is considered sufficient to implicate Cr(V) as the ultimate carcinogenic form of carcinogenic chromium compounds. (11 Refs)

OTHER METABOLISM OF CARCINOGENS

9. MEMBRANE-BOUND SIALOGLYCOPROTEINS FROM RAT LIVER AFTER COMBINED EXPOSURE TO BENZO(A)PYRENE AND SULFUR DIOXIDE.

Merkur'eva RV, Bushinskaia LI, Skvortsova NN, Dolinskaia SI, Shaternikova IS, Nozdracheva LI
Lab. Biochemistry and Hygiene of Atmospheric Pollutants, A. N. Sysin Inst. General and Community Hygiene, Moscow, USSR
Vopr Med Khim; 27(6):791-794 1981

The effect of carcinogens on metabolism of membrane-bound sialoglycoproteins (MBSGP) was studied in random-bred albino male rats. Animals were exposed to benzo(a)pyrene (BP) in combination with sulfur dioxide (SD). Within 2 wk, 6 wk, and 6 mo after exposure, rats were sacrificed and the distribution of MBSGP in the liver was determined. Combined exposure to BP and SD resulted in the increase of N-acetylneuraminic acid content in liver mitochondria and liver lysosomes, decrease of neuraminidase activity, and increase of beta-galactosidase activity. Carcinogens did not affect lipid peroxidation in the liver tissue. (20 Refs) (In RUS)

10. FORMATION OF N-(GLUTATHION-S-METHYLENE)-4-AMINOAZOBENZENE FOLLOWING METABOLIC OXIDATION OF THE N-METHYL GROUP OF THE CARCINOGEN, N-METHYL-4-AMINOAZOBENZENE.

Ketterer B, Srai SK, Waynforth B, Tullis DL, Evans FE, Kadlubar FF
Courtauld Inst. Biochemistry, Middlesex Hosp. Medical Sch., London W1P 7PN, England
Chem Biol Interact; 38(3):287-302 1982

A major biliary metabolite of the hepatocarcinogen, N,N-dimethyl-4-aminoazobenzene (DAB), in the rat was identified as N-(glutathion-S-methylene)-4-aminoazobenzene (GS-CH2-AB). This conjugate was prepared synthetically by a Mannich condensation of 4-aminoazobenzene (AB), formaldehyde (CH2O) and glutathione (GSH) and has been characterized by chemical analysis and by ultraviolet, visible and 13C-NMR spectroscopy. The same conjugate was also formed in vitro by incubating N-methyl-4-aminoazobenzene (MAB), NADPH, NADH and GSH with rat hepatic microsomes. Evidence is presented that GSH reacted with an intermediate resulting from a cytochrome P-450-dependent oxidation of the N-methyl substituent. This reactive intermediate is presumed to be either an N-methylol or a methimine derivative of AB. The significance of this detoxification mechanism is discussed. The presence of an additional major aminoazo-dye GSH conjugate is also noted. (Author abstract) (31 Refs)

11. FORMATION AND IDENTIFICATION OF GLUTATHIONE CONJUGATES FROM 2-NITROSOFLUORENE AND N-HYDROXY-2-AMINOFLUORENE.

Mulder GJ, Unruh LE, Evans FE, Ketterer B, Kadlubar FF
(c/o Kadlubar) Natl. Center Toxicological Res., Dept. Health and Human Services, Jefferson, AR, 72079
Chem Biol Interact; 39(1):111-127 1982

The compounds 2-nitrofluorene (NOF) and N-hydroxy-2-aminofluorene (N-HO-AF) are potent direct-acting mutagens, derived from metabolic activation of the carcinogen, N-acetyl-2-aminofluorene (AAF). To assess the ability of cellular glutathione (GSH) to detoxify these electrophilic derivatives, we examined the reaction of NOF and N-HO-AF with GSH in vitro. Two reaction products were isolated and identified as glutathionyl derivatives of 2-amino-fluorene (AF) containing an N-S linkage. Amino acid analysis, infrared and NMR (500 MHz) spectroscopy, fast atom bombardment mass spectrometry and analysis of reaction characteristics and hydrolysis products established their structures as N-(glutathion-S-yl)-2-aminofluorene S-oxide (GS-AFI) and N-(glutathion-S-yl)-2-aminofluorene (GS-AFII). Ascorbic acid, which reduces NOF to N-HO-AF, was used to modify reaction yields. These results indicated that GS-AF1 was derived from reaction with NOF and that GS-AFII could be formed from both NOF and N-HO-AF. A reaction scheme is proposed in which NOF reacts with GSH to form an intermediate addition product that can rearrange either to GS-AF1 or be reduced to GS-AFII. The latter could also be formed by direct reaction with N-HO-AF. (Author abstract) (50 Refs)

MODIFICATION OF CARCINOGEN METABOLISM

12. METABOLISM OF BENZO[A]PYRENE BY GUINEA PIG ADRENAL AND HEPATIC MICROSOMES.

Colby HD, Johnson PB, Pope MR, Zulkoski JS
Dept. Physiology, West Virginia Univ. Sch. Medicine, Morgantown, WV, 26506
Biochem Pharmacol; 31(5):639-646 1982

Studies were carried out to compare the metabolism of benzo[a]pyrene (BP) by adrenal and hepatic microsomes obtained from adult male guinea pigs. Adrenal microsomes produced fluorescent metabolites (primarily phenols) approx three to four times more rapidly than hepatic microsomes, but the differences in the rates were considerably smaller when total BP metabolism was assessed using an isotopic assay. The apparent discrepancy between the two assays is attributable to differences in the profiles of BP metabolites produced by adrenal and liver. Separation of metabolites by high pressure liquid chromatography revealed that adrenal microsomes converted BP to primarily a phenolic metabolite with a retention time identical to that of 3-hydroxy-BP. Liver microsomes, by contrast, produced approx equal amounts of compounds co-chromatographing with 3-hydroxy-BP and BP-4,5-dihydrodiol. Small amounts of other metabolites were also produced by adrenal and hepatic microsomes. Liver microsomes catalyzed the conversion of BP to metabolites that became covalently bound to exogenous DNA. The amount of binding was dependent upon the duration of incubation and concentration of microsomal protein. Adrenal microsomes, by contrast, did not promote BP binding to DNA. Inhibition of microsomal epoxide hydratase activity with trichloropropene oxide (TCPO) blocked the formation of dihydrodiol metabolites of BP by adrenal and liver microsomes. In the presence of TCPO, liver microsomes produced large amounts of a BP metabolite co-chromatographing with BP-4,5-oxide. TCPO also increased the rate of production of DNA-binding metabolites by liver microsomes but had no effect on the formation of DNA-binding metabolites by adrenal microsomes. The results demonstrated major differences in the pathways of BP metabolism by guinea pig adrenal and hepatic microsomes. Although adrenal microsomes metabolize BP more rapidly than hepatic microsomes, far greater amounts of reactive metabolites are produced by the liver. Thus, adrenal metabolism of BP may be of little toxicological significance. (Author abstract) (48 Refs)

13. VARIATION IN METABOLISM OF BENZO[A]PYRENE IN EPIDERMAL KERATINOCYTES AND DERMAL FIBROBLASTS OF HUMANS AND MICE.

Kuroki T, Hosomi J, Nemoto N

Dept. Pathobiochemical Cell Res., Inst. Medical Science, Univ. Tokyo, Shirokanedai, Minato-ku, Tokyo 108, Japan

Gann Monogr Cancer Res; 27:59-71 1982

Metabolism of benzo[a]pyrene (BP) in human epidermal keratinocytes (HEK) from normal subjects was investigated. BP is metabolized by a substrate-inducible cytochrome P-448-linked mixed-function oxygenase or aryl hydrocarbon hydroxylase (AHH). AHH activity was assayed by measuring formation of 3-hydroxy-benzo[a]pyrene (3-hydroxy-BP) from BP after incubation in reaction mixture containing cell homogenate, NADPH, and magnesium ions. The av value of noninduced basal AHH in six cultures of HEK was 3.3 picomoles equivalent of 3-hydroxy-BP/mg protein/hr and varied between 1.2 and 4.4. The variation in BP metabolism was studied in pairs of cultures of HEK and dermal fibroblasts, each isolated from the same subject. Dermal fibroblasts metabolized BP to a lesser extent than HEK, with the av basal AHH activity of three samples being 1.4 picomoles/mg protein/hr, and the ratio of the induced level to basal level being 4-6. Total metabolism of BP was low in dermal cells: 20-30% of added BP was metabolized in 48 hr in dermal fibroblasts, while 90% was metabolized by HEK in 48 hr under the same conditions. When HEK were cocultured with V79 Chinese hamster cells in the presence of BP, mutation was induced only with epidermal cells were used as the activating layer. Dermal fibroblasts did not activate BP to a mutagenic form(s) in cocultured V79 cells. Mouse dermal fibroblasts can activate BP and produce mutation in cocultured V79 cells. HEK have lower activities of uracil diphosphate-glucuronyl transferase and sulfate transferase than rodent embryo cells. (45 Refs)

14. DIFFERENTIAL EFFECTS OF DIETARY BHA ON HEPATIC ENZYME ACTIVITIES AND BENZO[A]PYRENE METABOLISM IN MALE AND FEMALE NMRI MICE.

Dock L, Cha YN, Jernstrom B, Moldeus P
Dept. Forensic Medicine, Karolinska Inst., Box 60400, S-104 01 Stockholm 60, Sweden
Carcinogenesis; 3(1):15-19 1982

The effect of dietary 2(3)-tert-butyl-4-hydroxy-anisole (BHA) alone and in combination with intraperitoneal injections of 3-methylcholanthrene (MC), on hepatic enzyme activities and benzo[a]pyrene (BP) metabolism was compared in male and female NMRI mice. In general, the characteristic induction pattern following dietary BHA administration in female mice could also be seen when male mice were used. The increase in epoxide hydrolase and cytosolic glutathione S-transferase following BHA feeding was however not as pronounced in males as in females. Also, MC treatment appeared to counteract the induction of GST activity by BHA in females but not no such effect in males. Liver microsomes from untreated male mice catalyzed the metabolism of BP less efficiently than did microsomes from females. BHA treatment increased this activity in both sexes to a comparable extent and the overall activity was the same in males and females having received MC. The pattern of BP metabolites was altered following BHA treatment. In general, an increase in BP-4,5-diol and a decrease in 9-OH-BP was observed. This pattern was also noticed when microsomes from MC treated and MC BHA treated animals were compared. MC treatment alone increased the amount of BP-7,8-diol, the quinones and the phenols. The present report indicates that several factors may contribute to the response to dietary BHA in mice. Whether this has any consequence in regard to this compound's anticarcinogenic effect remains to be elucidated. (Author abstract) (32 Refs)

15. THE EFFECTS OF DIETARY SELENIUM ON THE BIOTRANSFORMATION OF 7,12-DIMETHYLBENZ[A]ANTHRACENE.

Schillaci M, Martin SE, Milner JA
(c/o Martin) Dept. Food Science, Univ. Illinois, Urbana, IL, 61801
Mutat Res; 101(1):31-37 1982

Effects of dietary selenium on mutagenicity of 7,12-dimethylbenz[a]anthracene (DMBA) following incubation with liver microsomes from Sprague-Dawley rats given Se in drinking water (5 ppm) or in the diet (0.1, 2.5, or 5 ug/g) for 3 wk were investigated. All rats also received 0, 20, 50, 100 or 500 mg Aroclor 1254/kg body wt. Addition of Se to the drinking water significantly reduced final body wt of the rats and increased plasma Se. S9 liver microsome preparations from the rats did not differ in Se content. The number of revertants in the Salmonella typhimurium test increased approx 280% when the amount of Aroclor was increased from 20 to 100 mg/kg. Livers from rats induced with Aroclor (20-100 mg/kg) receiving Se had a reduced ability of S9 preparations to induce transformation of DMBA (71 and 31% reductions in the number of revertants compared with controls at the 20-and 100-mg/kg induction levels, respectively). Se supplementation of the diet significantly reduced the capability of the rat-liver fractions to transform DMBA. With 2.5 ppm Se, the number of revertants/plate decreased from 68 to 37 at the 20-mg/kg level of Aroclor induction. At 50 and 100 mg/kg induction levels, colonies/plate decreased from 159 to 18 and 136 to 41, respectively. Se at 5 ppm reduced the number of revertants/plate from 68 to 20, 154 to 51, and 136 to 47, at the 20-, 50-, and 100-mg/kg induction levels of Aroclor, respectively. Thus, in vivo Se supplementation may reduce susceptibility to various carcinogens. (24 Refs)

16. MULTIPLE DRUG METABOLISM: P-NITROANISOLE REVERSAL OF ACETONE ENHANCED ANILINE HYDROXYLATION.

Bidlack WR, Lowery GL
Dept. Pharmacology and Nutrition, Univ. Southern California, Sch. Medicine, 2025 Zonal Ave., Los Angeles, CA, 90033
Biochem Pharmacol; 31(3):311-317 1982

The unique effect of acetone on the p-hydroxylation of aniline was evaluated in microsomes prepared from control, phenobarbital- and 3-methylcholanthrene-pretreated animals. The existence of multiple forms of the hydroxylase was evaluated as an explanation of the acetone enhancement. Simultaneous metabolism of aniline in the presence of either p-nitroanisole (pNA) or ethylmorphine (EM) was evaluated to probe the participation of different mixed function oxidase systems. Aniline inhibited both N- and O-demethylation, while pNA and EM both inhibited p-hydroxylation of aniline. Acetone decreased the individual demethylation reactions, but enhanced aniline hydroxylation. In multiple drug reactions, acetone decreased N-demethylation and proportionately increased aniline p-hydroxylation. On the other hand, p-nitroanisole blocked the acetone enhancement of aniline metabolism. Kinetic evaluation of the acetone and p-nitroanisole effects on aniline metabolism indicated that each agent increased the apparent Km' by four- to five-fold for aniline in the hydroxylation reaction, but only acetone increased the Vmax'. From the Eadie-Scatchard analysis of the rates of aniline hydroxylation, acetone appeared to produce a biphasic increase in the hydroxylation above 0.75 mM aniline, even in the presence of pNA. Thus, multiple forms of the aniline p-hydroxylase are indicated by their altered activities in the presence of other drugs, and acetone seemed to specifically alter a species having a higher Km' for aniline. (Author abstract) (35 Refs)

17. CYCLIC NUCLEOTIDE MODULATION OF IN VITRO MORPHOLOGICAL TRANSFORMATION OF SYRIAN HAMSTER CELLS.

Mironescu SG, Epstein SM, DiPaolo JA
Dept. Pathology, Univ. South Carolina Sch. Medicine, Columbia, SC, 29208
Cancer Res; 42(4):1274-1278 1982

The cyclic nucleotides, cyclic adenosine 3':5'-monophosphate (cAMP) and cyclic guanosine 3':5'-monophosphate (cGMP) or their dibutyryl and monobrominated derivatives, may either increase or decrease morphological transformation of Syrian hamster embryo cells exposed to N-methyl-N'-nitro-N'-nitrosoguanidine (MNNG). The effect on transformation is primarily a function of the parent cyclic nucleotide and the duration of exposure to the nucleotides. At concentrations of 5 mM or larger for a minimum 24-hr exposure cAMP, cGMP, and their congeners reduced the colony-forming ability of nontransformed Syrian hamster embryo cells not exposed to MNNG; however, cGMP and its derivatives caused less toxicity than cAMP or its analogs. cAMP and its monobrominated and dibutyrylated derivatives decreased the transformation frequency associated with MNNG irrespective of whether the various adenylnucleotides were administered before or after MNNG. The greatest inhibitory effect on MNNG-induced transformation was obtained with N6,O2-dibutyryl cyclic adenosine 3':5'-monophosphate followed in order by 8-bromocyclic adenosine 3':5'-monophosphate and cAMP. At equimolar doses, the dibutyryl and brominated analogs of cGMP but not unsubstituted cGMP enhanced transformation when administered prior to exposure of the Syrian hamster embryo cells to MNNG but reduced the transformation frequency when added

after MNNG. The enhancing and inhibitory effects of the guanine cyclic nucleotide-induced alteration of MNNG-associated transformation frequencies were dose and time dependent and occurred in the order N6,O2-dibutyryl cyclic guanosine 3':5'-monophosphate great er than 8-bromocyclic guanosine 3':5'-monophosphate very much greater than cGMP. Butyric acid neither diminished nor increased MNNG-induced transformation frequency. The latter suggests that butyrate ions formed by metabolism of the cyclic nucleotide analogs were not a factor in the observed alterations of transformation frequency. (Author abstract) (35 Refs)

18. DECREASED CYTOTOXICITY OF CIS-DIAMMINEDICHLOROPLATINUM(II) BY ALPHA-DIFLUOROMETHYLORNITHINE DEPLETION OF POLYAMINES IN 9L RAT BRAIN TUMOR CELLS IN VITRO.

Oredsson SM, Deen DF, Marton LJ
(c/o Marton) Editorial Office, Dept. Neurological Surgery, Univ. California, 350 Parnassus Ave., Suite 807, San Francisco, CA, 94117
Cancer Res; 42(4):1296-1299 1982

Before treatment with the cytotoxic drug cis-dichlorodiammineplatinum(II) (cis-platinum), 9L rat brain gliosarcoma cells grown in vitro were depleted of intracellular polyamines by alpha-difluoromethylornithine (DFMO; 10 mM, 48 hr), an enzyme-activated, irreversible inhibitor of the polyamine-synthetic enzyme ornithine decarboxylase. In contrast to studies that showed that the cytotoxicity of 1,3-bis (2-chloroethyl)-1-nitrosourea as measured by colony-forming efficiency is enhanced by DFMO depletion of intracellular polyamines, the cytotoxicity of cis-platinum was significantly decreased in polyamine-depleted 9L cells. At 10, 1, and 0.1% survival levels the dose modification factors were 2.0 to 2.1. Addition of exogenous putrescine to polyamine-depleted 9L cells 24 hr before treatment with cis-platinum partially reversed this phenomenon. When 9L cells were treated either with DFMO and cis-platinum or with DFMO, putrescine, and cis-platinum for 1 hr, a time period that is too short for DFMO to affect intracellular polyamine levels, the cytotoxicity of cis-platinum was decreased, but to a significantly lesser extent than by the 48 hr DFMO pretreatment. Putrescine alone did not alter the cytotoxic effect of cis-platinum when administered either 24 or 1 hr before treatment. DFMO appears to affect cis-platinum cytotoxicity by two different mechanisms, the first mediated through polyamine depletion and the second through a direct interaction with cis-platinum. (Author abstract) (29 Refs)

19. EFFECTS OF DIETARY SELENIUM ON THE METABOLISM AND EXCRETION OF 2-ACETYLAMINOFLUORENE IN THE RAT.

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J Toxicol Environ Health; 9(1):63-76 1982

Effects of selenium on metabolism of 2-acetylaminofluorene (AAF) in male weanling CD rats were investigated. Animals were fed either a diet deficient in Se or the same diet supplemented with 0.5 ppm Se as sodium selenite. Hepatic microsomal metabolism of [9-14C]AAF (1 mCi/millimole) was measured in vitro. Microsomes from Se-deficient rats generated significantly less 3-OH-AAF than those from Se-supplemented animals. Only small amounts of N-OH-AAF were produced and no difference was noted between the two groups of animals. Moderately increased activity of glucuronyltransferase occurred in Se-deficient rats while hepatic soluble sulfotransferase activity was the same in both groups. Se-deficient rats excreted more of the given dose of AAF than did Se-supplemented rats; the increase was due to glucuronic acid- and sulfuric acid-conjugated metabolites and non-ether-extractable, water-soluble metabolites. Se-deficient rats excreted more N-OH-AAF, 7-OH-AAF, and 3-OH-AAF, while Se-supplemented rats excreted more 5-OH-AAF. Se-deficient rats excreted more of the administered dose of AAF as 7-OH-AAF than did Se-supplemented animals. A protective effect of dietary Se against AAF-induced hepatocarcinogenesis may be due in part to the inhibition of N-hydroxy-AAF production in vivo. (45 Refs)

20. RETINOL (VITAMIN A) AS A MODIFIER OF 2-AMINOFLUORENE AND 2-ACETYL-AMINOFLUORENE MUTAGENESIS IN THE SALMONELLA/MICROSOME ASSAY.

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Arch Toxicol; 49(2):169-174 1982

Vitamin A (retinol) has been demonstrated to modify the mutagenic activity of the aromatic amines, 2-aminofluorene (2AF) and 2-acetylaminofluorene (2AAF) when added to the Ames Salmonella/mammalian microsome assay. Low amounts of retinol (2-20 ug/plate) increased the mutagenicity of both 2AF and 2AAF. At higher doses (50-150 ug/plates) the mutagenicity of 2AAF remained unchanged while the mutagenicity of 2AF gradually decreased. The present data do not support the hypothesis that retinol generally acts as an inhibitor of in vitro metabolic activation of procarcinogens. (Author abstract) (16 Refs)

21. RETINOL (VITAMIN A) INHIBITS SISTER CHROMATID EXCHANGES AND CELL CYCLE DELAY INDUCED BY CYCLOPHOSPHAMIDE AND AFLATOXIN B1 IN CHINESE HAMSTER V79 CELLS.

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Carcinogenesis; 3(1):1-5 1982

Retinol (vitamin A alcohol) at the doses tested neither induced an increase of frequency of sister chromatid exchanges (SCE) nor cell cycle delay in Chinese hamster V79 cells with or without the metabolic activation of S-9 mix. However, it inhibited SCE frequencies and cell cycle delay in V79 cells induced by the indirect mutagen cyclophosphamide or aflatoxin B1. The inhibition was found to be dose and time dependent. These results suggest that retinol itself may have no direct effect on the genetic materials but rather exert its effects possibly by inhibiting the metabolic activation of an indirect mutagen or carcinogen. Thus, the antitumor activities of retinoids may not be limited to the widely accepted role of the preventing the promotion step but also the initiation step of carcinogenesis. (Author abstract) (33 Refs)

22. RETINOIC ACID MODULATION OF ULTRAVIOLET LIGHT-INDUCED EPIDERMAL ORNITHINE DECARBOXYLASE ACTIVITY.

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J Invest Dermatol; 78(2):121-124 1982

Irradiation of skin with UV light of sunburn range (UVB) leads to a large and rapid induction of the polyamine biosynthetic enzyme ornithine decarboxylase in the epidermis. Induction of epidermal ornithine decarboxylase also occurs following application of the tumor promoting agent 12-O-tetradecanoylphorbol-13 acetate and topical retinoic acid is able to block both this ornithine decarboxylase induction and skin tumor promotion. In the studies described below, topical application of retinoic acid to hairless mouse skin leads to a significant inhibition of UVB-induced epidermal ornithine decarboxylase activity. The degree of this inhibition was dependent on the dose, timing, and frequency of the application of retinoic acid. To show significant inhibition of UVB-induced ornithine decarboxylase the retinoic acid had to be applied within 5 hr of UVB irradiation. If retinoic acid treatment was delayed beyond 7 hr following UVB, then no inhibition of UVB-induced ornithine decarboxylase was observed. The quantities of retinoic acid used (1.7 nmol and 3.4 nmol) have been shown effective in inhibiting 12-O-tetradecanoyl phorbol-13 acetate induced ornithine decarboxylase. The results show that these concentrations of topical retinoic acid applied either before or immediately following UVB irradiation reduces the UVB induction of epidermal ornithine decarboxylase. The effect of retinoic acid in these regimens on UVB-induced skin carcinogenesis is currently under study. (Author abstract) (20 Refs)

MUTAGENICITY OF ACTIVATED METABOLITES OF CARCINOGENS

23. CYTOGENETIC EFFECTS ON THE EASTERN MUDMINNOW, UMBRA PYGMAEA, EXPOSED TO ETHYL METHANESULFONATE, BENZO[A]PYRENE, AND RIVER WATER.

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Ecotoxicol Environ Saf; 5(3):261-269 1981

The eastern minnow, Umbra pygmaea, was exposed to two known genotoxic agents and to water from the Rhine river at Lobith, The Netherlands. Both chromosome aberrations and sister chromatid exchanges (SCE) were scored. Fish were exposed to 0, 8, 40, and 200 mg ethylmethanesulfonate (EMS)/liter and 0, 10(-5), and 10(-4) mg benzo[a]pyrene (BaP)/liter at 20 C for 48 hr. Two additional groups of fish were exposed to 10(-4) mg/liter BaP for 4 and 6 days. EMS induced chromatid breaks, chromosome breaks, and gaps in gill and fin tissue; most of the aberrations were chromatid aberrations. EMS concentrations of 8, 40, and 200 mg/liter induced 1.1, 6.8, and 19.6% metaphases with aberrations, respectively. BaP only induced chromosome aberrations in fish exposed to the higher concentration; both chromatid breaks and gaps were seen. Activity of benzo[a]pyrene hydroxylase was near the detection limit (0.01 umole/g liver/hr). Bromodeoxyuridine injection to improve the number of metaphases with differential staining gave best results in gill tissue after two or three injections. Rhine water induced chromosome aberrations (chromatid breaks, chromosome breaks, gaps) and increased the number of SCE/metaphase. U pygmaea was suitable for detecting cytogenetic effects of chemical pollution in the aquatic environment. (18 Refs)

24. ANALYSIS OF FECES FOR BENZO[A]PYRENE AFTER CONSUMPTION OF CHARCOAL-BROILED BEEF.

Hecht SS, LaVoie EJ, Goldin BR, Magee PN, Bruce WR, Van Soest PJ, Balish E
American Health Foundation, Naylor Dana Inst. for Disease Prevention, Valhalla, NY, 10595
Banbury Rep; 7:381-391 1981

Rat and human studies on the excretion of benzo[a]pyrene (BaP) and its metabolites after consumption of charcoal-broiled beef are reported. Fecal excretion of BaP was 11% of the dose given to rats fed meat containing 52.7 ug/kg BaP. With humans, each subject consumed approx 8.6 ug BaP. Excretion of approx 0.9 ug unchanged BaP per person was expected based on the rat studies. However, BaP levels in the human feces were less than 0.1 ug/person. Possible explanations for these findings are discussed. (31 Refs)

25. INACTIVATION OF A DIOL EPOXIDE BY DIHYDRODIOL DEHYDROGENASE BUT NOT BY TWO EPOXIDE HYDROLASES.

Glatt HR, Cooper CS, Grover PL, Sims P, Bentley P, Merdes M, Waechter F, Vogel K, Guenthner TM, Oesch F
Inst. Pharmacology, Obere Zahlbacher Strasse 67, D-6500 Mainz, W. Germany
Science; 215(4539):1507-1509 1982

The mutagenicity of r-8,t-9-dihydroxy-5-10,11-oxy-8,9,10,11 tetrahydrobenz[a]anthracene (BA-8,9-diol 10,11-oxide) toward Salmonella typhimurium TA 100 is not decreased by the presence of large amounts of highly purified microsomal or cytosolic epoxide hydrolase. However, highly purified dihydrodiol dehydrogenase inactivates this diol epoxide, which is a major DNA-binding metabolite of benz[a]anthracene. The K-region epoxide, benz[a]anthracene 5,6-oxide (BA 5,6-oxide) is efficiently inactivated by microsomal epoxide hydrolase, is much less readily inactivated by cytosolic epoxide hydrolase, and is not inactivated by dihydrodiol dehydrogenase. This inactivation of a diol epoxide by dihydrodiol dehydrogenase points to a new significance of this enzyme and a new level of control for diol epoxides. (Author abstract) (32 Refs)

26. INDUCTION OF 6-THIOGUANINE-RESISTANT MUTATIONS BY RAT-LIVER HOMOGENATE (S9)-ACTIVATED PROMUTAGENS IN HUMAN EMBRYONIC SKIN FIBROBLASTS.

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Mutat Res; 101(1):87-98 1982

A quantitative mutation assay consisting of early passage of cultured human fibroblasts together with an exogenous rat liver microsomal preparation to activate promutagens capable of inducing cytotoxic and mutagenic responses is described. Optimal conditions for a 6-thioguanine (6-TG) resistance mutation assay in the diploid human embryonic skin fibroblast strain (GM10) were investigated. The promutagens used were benzo[a]pyrene (BaP), 3-methylcholanthrene (3MC), and dimethylnitrosamine (DMN). At a constant amount of S9 protein concentration, a linear correlation between mutagenicity and dose was observed. At 50% survival, the mutation frequencies of BaP and 3MC 3MC (5 ug/ml) were 60 and 30x the background frequency, respectively, and DMN (5 mg/ml) induced 6-TG mutant frequencies 25x more than background. 3MC and BaP (5 ug/ml) decreased the colony-forming ability of GM10 to 50 and 20%, respectively; DMN at concentrations of 1 and 5 mg/ml inhibited colony-forming ability between 20 and 60%. At high S9 concentrations a deactivation or detoxification phenomenon was observed. When the mutagenic efficiency of S9-activated chemicals was plotted as the number of induced mutations vs log survival it was not affected by the deactivation capacity of S9 proteins. (42 Refs)

27. INFLUENCE OF LIVER S-9 PREPARATIONS FROM RATS AND RAINBOW TROUT ON THE ACTIVITY OF FOUR MUTAGENS.

De Flora S, Zanacchi P, Bennicelli C, Arillo A
Inst. Hygiene, Sch. Medicine, Univ. Genoa, 16132 Genoa, Italy
Toxicol Lett; 10(4):345-349 1982

The effects of rat and trout liver post-mitochondrial fractions on benzo(a)pyrene (BP), 2-aminofluorene (2-AF), aflatoxin B1 (AFB1), and sodium dichromate in the Ames reversion assay were compared. Rat preparations were significantly more efficient in activating AFB1 and 2-AF. Rat and trout preparations were equally effective in decreasing the direct mutagenicity of sodium dichromate. Rat microsomes were virtually ineffective and trout preparations were slightly active in producing mutagenic metabolites from BP. (14 Refs)

28. INITIATION AND PROMOTION, MUTAGENESIS AND TRANSFORMATION OF C3H/10T1/2 MOUSE EMBRYO FIBROBLASTS.

Heidelberger C
Univ. Southern California Sch. Medicine, Los Angeles, CA, 90031
Gann Monogr Cancer Res; 27:207-219 1982

The C3H/10T1/2 mouse embryo fibroblast cloned cell line is discussed with respect to initiation and promotion, mutagenesis, and transformation. Transformation by polycyclic aromatic hydrocarbons was dose-dependent and did not involve activation of an endogenous retrovirus or its cores or RNA. Metabolism of benzo[a]pyrene in microsomes of these cells involves formation of 7,8-and 9,10-d iols, phenols and quinones. UV light is a pure initiator, x-rays initiate transformation, and saccharin in a weak promoter. While 12-O-tetradecanoyl phorbol-13-acetate (TPA) is strongly mitogenic and produces hyperplasia in mouse skin, it does not significantly increase the saturation density of C3H/10T1/2 cells. All chemical classes of tumor promoters are not suitable for screening by measuring their effects on the 5-azacytidine-induced differentiation of C3H/10T1/2 cells because of inconsistencies in results. Mutagenic and oncogenic transformation in these cells is described. Mutagenesis data can be interpreted in various ways in order to obtain the desired result. In this system mutagenesis appears to be necessary but is not sufficient for transformation. (60 Refs)

29. THE RESPONSE OF A VARIETY OF HUMAN FIBROBLAST CELL STRAINS TO THE LETHAL EFFECTS OF ALKYLATING AGENTS.

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Carcinogenesis; 3(1):33-37 1982

The sensitivities of 15 human fibroblast cell strains to the lethal effects of alkylation damage produced by N-methyl-N-nitrosourea (MNU) and N-ethyl-N-nitrosourea (ENU) have been investigated. Nine cell strains were also investigated for their sensitivities to N-methyl-N'-nitro-N-nitrosoguanidine (MNNG). Included in our survey are representative strains derived from donors with the repair defective syndromes xeroderma pigmentosum (XP) and ataxia-telangiectasia (A-T), as well as strains derived from patients with Cockayne's syndrome, Bloom's syndrome, Huntington's disease and strains derived from individuals with unclassified syndromes. On the basis of our survival data we report that hypersensitivity to MNU is shown by two A-T strains (AT3BI and AT5BI), an XP strain (XP3BR), and strain 46BR derived from a patient with hypogammaglobulinemia. This sensitivity to methylating agents is also shown by strains 46BR and XP3BR when treated with MNNG, but not for strain AT5BI. Sensitivity to ENU is shown by strain 11961 (derived from a sun-sensitive individual), XP3BR and a single Cockayne's syndrome strain CS697CTO. Of the strains studied only XP3BR was sensitive to both ethylating and methylating agents and only 46BR showed a greater than two-fold increase in sensitivity compared to normal. (Author abstract) (45 Refs)

30. COMPARISONS BETWEEN CARCINOGENIC POTENCY AND MUTAGENIC POTENCY TO SALMONELLA IN A SERIES OF DERIVATIVES OF 4-DIMETHYLAMINOAZOBENZENE (DAB).

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Mutat Res; 93(1):67-81 1982

The carcinogenic and mutagenic potencies of 4-dimethylaminoazobenzene (DAB) and several derivatives of DAB were compared. Test compounds were 5-phenylazoindazole (5I), 6-phenylazoindazole (6I), 7-phenylazoindazole (7I), 5-phenylazobenzothiazole (5BT), 6-phenylazobenzothiazole (6BT), and 7-phenylazobenozothiazole (7BT). Reference compounds were DAB, the noncarcinogen 4'-dimethylamino-4-dimethylaminoazobenzene (Compound II), and the potent carcinogen 2'3'-dimethyl-4-dimethylaminoazobenzene (Compound III). S9 mix was prepared from livers of male Sprague-Dawley rats treated with Aroclor 1254. Mutagenicity was measure in Salmonella typhimurium strain TA98 in plate-incorporation (PI), liquid pre-incubation (LPI), and fluctuation tests. DAB, 5I, and 6BT were tested by ip injection into Alderley Park rats; liver tissue was examined 6 hr after injection. Results of the PI test were negative for DAB and positive for all other compounds. Results of the LPI test were positive for all compounds. The results of the fluctuation test were positive for DAB, 5I, 6I, 7I, 5BT, 6BT, and 7BT and negative for Compounds II and III. DAB and 6BT produced pathological changes in rat liver and affected the recovery profile of methylated bases derived from hepatic DNA of pretreated rats; 5I did not. The value of short-term in vivo assays, including the potential to identify potent mammalian carcinogens among structurally related compounds, is discussed. (45 Refs)

31. METABOLIC ACTIVATION AND MUTAGENICITY OF CARCINOGENIC N-NITRAMINES IN LIQUID-INCUBATION SYSTEM.

Khudolei VV, Bartsch H, Malaveille C
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International Agency Res. Cancer, Lyon, France
Vopr Onkol; 27(12):47-51 1981

The study established the mutagenicity of carcinogenic dimethylnitramine and nitromorpholine in a liquid-incubation system using Salmonella typhimurium TA 100 and TA 1530 as indicator, in the presence of hepatic postmitochondrial supernatant obtained from aroclor 1254-treated rats, oxygen and NADP - generating system. Synthesis of mutagenic metabolites of nitramines was in correlation with the level of N-dimethylase activity. Ascorbic acid and disulfiram efficiently inhibited intramune-induced mutagenesis. Metabolic activation of nitramines involves (a) conversion of nitramines to nitrosoamines due to reduction of a nitro group, (b) hydroxylation by means of multi-function oxidases, and (c) heterolysis resulting in the formation of an end metabolite which is actually responsible for carcinogenicity and mutagenicity. (Author abstract) (17 Refs) (In RUS)

32. MUTAGENICITY OF AZO DYES IN THE SALMONELLA/ACTIVATION TEST.

Robertson JA, Harris WJ, McGregor DB
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Carcinogenesis; 3(1):21-25 1982

The detection of certain bis-azo biphenyl dyes (Trypan blue, Evans blue and Congo red) by a modification of the standard Ames test protocol is reported. Detection of a mutagenic response required both the inclusion of FMN in S-9 mix and use of a static pre-incubation step prior to addition of top-agar and pouring in the usual manner. Evidence is presented to substantiate the proposal that use of this protocol provides optimal conditions for the two stages of activation required for the production of mutagenic metabolites from these dyes. These are (i) initial flavin-mediated (hepatic) azo reduction resulting in the formation of proximate mutagenic metabolites followed by (ii) the oxidative metabolism by S-9 resulting in the formation of ultimately mutagenic products. (Author abstract) (16 Refs)

33. MUTAGENS IN EXTRACTS OF GASTROINTESTINAL MUCOSA.

Stemmermann GN, Mower H, Rice S, Ichinotsubo D, Tomiyasu L, Hayashi T, Nomura A, Mandel M
Pathology Dept., Kuakini Medical Center, Honolulu, HI, 96817
Banbury Rep; 7:175-183 1981

Mucosal specimens from 60 resected stomachs (31 from stomach cancer patients) and 25 colons (11 from colon cancer patients) were assayed for the presence of mutagenic compounds in Salmonella typhimurium TA98 and TA100. The specimens for assay were not grossly involved with cancer. Nitrosated TA98 mutagens were identified in 32/60 stomach specimens, mostly from the antrum. Both sex and age seemed to play a role in determining whether the antral tissues contained mutagens. The TA98 mutagens derived from the antral mucosa were generally nitrosated derivatives of diazepam, hydroxyzine, and cimetidine (which had been used in anesthesia), which does not mean that these agents are carcinogenic in the stomach or any other organ. However, their presence in the stomach serves as a model for the in vivo generation of nitrosated mutagenic compounds. The metabolic process can occur in the absence of dietary nitrite, provided that the gastric epithelium is exposed to any one of a wide variety of amide precursors. These observations support the epidemiologic findings of an inverse correlation between stomach cancer and the intake of foods containing substances (eg, ascorbic acid and vitamin E) blocking the nitrosation process. The intestinal specimens yielded a wide variety of TA98 and TA100 mutagens, which were not characterized chemically. Some of these mutagens seemed to favor specific sites in the colon. (6 Refs)

34. IDENTIFICATION OF MUTAGENIC METABOLITES FORMED BY C-HYDROXYLATION AND NITROREDUCTION OF 5-NITROACENAPHTHENE IN RAT LIVER.

El-Bayoumy K, Hecht SS
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Cancer Res; 42(4):1243-1248 1982

The metabolism of the mutagen and carcinogen, 5-nitroacenaphthene, by the 9,000 x g supernatant from the livers of Aroclor-pretreated rats was studied. The major primary metabolites were 1-hydroxy-5-nitroacenaphthene and 2-hydroxy-5-nitroacenaphthene. These metabolites were oxidized to 1-oxo-5-nitroacenaphthene and 2-oxo-5-nitroacenaphthene, hydroxylated to cis-1,2-dihydroxy-5-nitroacenaphthene and trans-1,2-dihydroxy-5-nitroacenaphthene and reduced to 1-hydroxy-5-aminoacenaphthene and 2-hydroxy-5-aminoacenaphthene. Reduction of 1-and 2-oxo-5-nitroacenaphthene to 1-oxo- and 2-oxo-5-aminoacenaphthene was also observed. When incubations were carried out in a N2-enriched atmosphere (10% O2 in N2), the major metabolites were 1-hydroxy- and 2-hydroxy-5-nitroacenaphthene and 2-oxo-5-aminoacenaphthene. Selected metabolites were tested for mutagenicity toward Salmonella typhimurium TA98. The most mutagenic of the metabolites tested, in the presence or absence of rat liver 9,000 x g supernatant, were 1-hydroxy-5-nitroacenaphthene and 1-oxo-5-nitroacenaphthene. These results indicate that the 9,000 x g supernatant from the livers of Aroclor-pretreated rats is capable of catalyzing both the oxidation and reduction of 5-nitroacenaphthene and that the reduced derivatives of 1-hydroxy- or 2-hydroxy- or 1-oxo- or 2-oxo-5-nitroacenaphthene are proximate mutagens. (Author abstract) (22 Refs)

35. NITROSATION REACTIONS OF STOMACH MUCOSAL TISSUE OF THE HUMAN AND DOG.

Rice S, Ichinotsubo D, Stemmerman G, Hayashi T, Palumbo N, Sylvester S, Nomura A, Mower HI, Goldman P, Mower HF, Tannenbaum SR, Goldin BR, Fine DH, Hill MJ, Reddy BS, Hecht SS, Newmark H
Dept. Chemistry, Univ. Hawaii, Honolulu, HI. 96817
Banbury Rep; 7:185-203 1981

Gastric mucosa specimens from patients who had received hydroxyzine-HCl (HZ), diazepam (DP) and cimetidine before gastrectomy, were assayed for mutagens in Salmonella strains TA98, TA100, TA1535, and TA1537. Mutagenic activity was identified in 21/65 specimens. High pressure liquid chromatographic assays identified the mutagens as nitrosated metabolites of HZ and DP. The enzymes required to metabolize these agents were never found simultaneously in the same specimen. The antral mucosa seemed to be unique among human gastrointestinal tissues in its ability to produce nitrosated metabolites of HZ and DP. No metabolites of fenantyl were found in the human tissues. Specimens of gastric antral mucosa from dogs (without prior drug treatment) contained several mutagens, mostly of the TA98 direct-acting type, in about 20% of cases. A similar number of mutagens occurred in the lower colon mucosa. The enzymes of the canine antral mucosa were capable of nitrosating HZ, DP, and fenantyl. No mutagenic metabolites were identified when human or canine antral mucosa was incubated with cimetidine in vitro, or in the antrum of a dog treated with dinitrosocimetidine 24 hr previously, but chemically synthesized nitrosated analogs of cimetidine showed mutagenic activity in all Salmonella strains except TA98. No component of the diet or environment is known to be nitrosated by the enzyme system discovered in the human antral mucosa, but the experiments with canine tissues suggested that some dietary or environmental components probably do interact with the nitrosative metabolism of the gastric or colonic mucosa. (4 Refs)

36. COMPARATIVE MISONIDAZOLE METABOLISM IN ANAEROBIC BACTERIA AND HYPOXIC CHINESE HAMSTER LUNG FIBROBLAST (V-79-473) CELLS.

Koch RL, Rose C, Rich TA, Goldman P
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Biochem Pharmacol; 31(3):411-414 1982

The metabolism of the radiation sensitizer misonidazole was similar in anaerobic cecal contents and hypoxic Chinese hamster lung fibroblasts (V-79-473). Both systems formed the amino derivative of misonidazole, [1-(2-aminoimidazol-1-yl)-3-methoxypropan-2-ol] (AIM), and urea, as well as a metabolite, (2-hydroxy-3-methoxypropyl)-guanidine (G), which has not been described previously. It appears that the nitro group of misonidazole was reduced to form AIM and that this compound was then hydrolyzed to yield either urea or G, the latter in yields of 25% (tissue culture) to 55% (cecal contents). When tested with the Ames tester strain, both G and AIM were slightly mutagenic only for strain TA 98 and then only in the presence of the system for microsomal activation. (Author abstract) (11 Refs)

37. NEOPLASTIC TRANSFORMATION OF HUMAN DIPLOID FIBROBLASTS TREATED WITH CHEMICAL CARCINOGENS AND CO-60 GAMMA-RAYS.

Namba M, Nishitani K, Fukushima F, Kimoto T, Utsunomiya J, Hayflick L
Dept. Pathology, Kawasaki Medical Sch., Matsushima 577, Kurashiki 701-01, Japan
Gann Monogr Cancer Res; 27:221-230 1982

Transformation of four strains of normal human fibroblasts with repeated treatment with 4-nitroquinoline 1-oxide (4NQO) and two strains with 60Co gamma-rays is reported. Single treatment with those agents had no such effect. A total of 256 experiments were conducted, 116 with 4NQO and 49 with 60Co gamma rays. The transformed cell lines had the following features: epithelial-like morphology, unlimited growth potential, abnormal karyotypes (heteroploid), increased saturation density, reduced growth inhibition by theophylline, increased lactate dehydrogenase isozyme B(H)/A(M) ratio, no large external transformation sensitive protein, elevated colony formation in soft agar, and a low serum requirement for growth. When unlimited growth and abnormal karyotypes are present, neoplastic transformation in human cells is indicated. Criteria of the morphology of transformed colonies were defined. Advantages and disadvantages of using normal human fibroblasts for transformation studies were discussed. Future considerations for the use of normal human fibroblasts for transformation studies were proposed. (21 Refs)

38. STIMULATION OF S-9 FRACTION METABOLISM IN RAT LIVER AND BREAST BY VITAL DYES.

Silva MH, Lee RE, Petrakis NL
Dept. Epidemiology and International Health, Univ. California, San Francisco, CA, 94143
Toxicol Lett; 10(2/3):205-208 1982

Known mutagens metabolized in rat liver and breast supernatant fractions were used in the Ames test to assess metabolizing enzyme induction by vital dyes. The mutagen 2-aminoanthracene (2AA) showed a 70% activity increase with neutral red, an 89% increase with methylene blue, and a 49% increase with trypan blue in treated rat liver fractions. The lowest and greatest increase in mutagenic activity with liver fractions was seen with 6-aminochrysene and diaminofluorene, respectively. An activity increase in treated breast fractions was found only with 2AA. Liver tissue was more readily induced than mammary glands of midpregnant rats. (11 Refs)

39. MUTAGENICITY TESTING OF CHLORINATED BIPHENYLS AND CHLORINATED DIBENZOFURANS.

Schoeny R
Dept. Environmental Health, Univ. Cincinnati Medical Center, 3223 Eden Ave., Cincinnati, OH, 45267
Mutat Res; 101(1):45-56 1982

The Salmonella typhimurium/microsome assay of Ames was used to assay four chlorinated biphenyls and five chlorinated dibenzofuran compounds. None of the polychlorinated biphenyls (PCB: 4-chlorobiphenyl, 3,4,3',4'-tetrachlorobiphenyl, 2,4,2',4'-tetrachlorobiphenyl, and 2,4,6,2',4',6'-hexachlorobiphenyl) reverted any of the Salmonella tester strains, which included three DNA target sequences. Assays incorporating hepati extracts (S9s) from rats treated with various inducing agents were also negative. Thus, S9 preparations from PCB-treated rats were not able to activate PCB components to detectably mutagenic forms in vitro. Dibenzofuran was assayed using dimethylsulfoxide as a solvent; the chlorinated derivatives were dissolved in a mixture of benzene:isooctane (1:9). Dibenzofuran, 2,9-dichlorodibenzofuran, 3,6-dichlorodibenzofuran, 2,3,7,8-tetrachlorodibenzofuran, and octachlorodibenzofuran were nonmutagenic for Salmonella strains TA98 and TA100 over a 3-log dose range with or without S9 activation. (37 Refs)

40. STUDIES ON METABOLISM AND TOXICITY OF STYRENE. IV. 1-VINYLBENZENE 3,4-OXIDE, A POTENT MUTAGEN FORMED AS A POSSIBLE INTERMEDIATE IN THE METABOLISM IN VIVO OF STYRENE TO 4-VINYLPHENOL.

Watabe T, Hiratsuka A, Aizawa T, Sawahata T, Ozawa N, Isobe M, Takabatake E
Lab. Drug Metabolism and Toxicolgy, Dept. Hygienic Chemistry, Tokyo Coll. Pharmacy, 1432-1 Horinouchi, Hachioji-shi, Tokyo 192-03, Japan
Mutat Res; 93(1):45-55 1982

The role of 1-vinylbenzene 3,4-oxide (VBO) in the metabolism of styrene to 4-vinylphenol and the mutagenicity of VBO in Salmonella typhimurium strains were studied. VBO had a half-life of 4.3 sec at pH 7.4 in aqueous soln. VBO was toxic to TA98 and TA100 strains, but was mutagenic only in TA100. VBO induced 7233 His revertant colonies/plate at a dose of 1.0 micromoles/plate. VBO was shorter-lived and more mutagenic than the 1,2-oxide. The vinylphenols formed from VBO and the 1,2-oxide were neither mutagenic nor cytotoxic. (24 Refs)

41. INVESTIGATION OF STYRENE IN THE LIVER PERFUSION/CELL CULTURE SYSTEM. NO INDICATION OF STYRENE-7,8-OXIDE AS THE PRINCIPAL MUTAGENIC METABOLITE PRODUCED BY THE INTACT RAT LIVER.

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Chem Biol Interact; 39(1):57-76 1982

Mutagenic effect of styrene and styrene-7,8-oxide was studied with the isolated perfused rat liver as metabolizing system and Chinese hamster V79 cells as genetic target cells. Styrene-7,8-oxide which is mutagenic per se was rapidly metabolized by the perfused rat liver. Thus no mutagenic effect was detected either in the perfusion medium or in the bile. However when styrene was added to the perfusion system, an increase in V79 mutants was observed regardless of where in the circulating perfusion medium the V79 cells were placed: the same effect was obtained with V79 cells close to the liver as well as at a distance from the liver. No mutagenic effect was observed in the bile. Simultaneous analysis of the styrene-7,8-oxide concentration in the perfusion medium, suggest that this metabolite is not the cause of the mutagenic effect observed during perfusion with styrene. The effect of the two test compounds on some liver functions was also studied. It is suggested that the results on styrene and styrene-7,8-oxide found here using the liver perfusion/cell culture system mimic the metabolism expected to be found in the intact animal, thus indicating that styrene-7,8-oxide is not the principal mutagenic metabolite of styrene in vivo. (42 Refs)

42. EVALUATION OF COAL LIQUEFACTION TECHNOLOGIES BY SALMONELLA MUTAGENESIS.

Warshawsky D, Shoeny R, Moore G
Dept. Environmental Health, Kettering Lab., 3223 Eden Ave., Cincinnati, OH, 45267
Toxicol Lett: 10(2/3):121-127 1982

Selected coal liquefaction materials were evaluated for mutagenicity in the Salmonella/microsome assay. Light oil products were found to be weakly or nonmutagenic. Heavy oils, such as vacuum bottoms, produced the greatest mutagenic activity. The separator bottoms and the filtered liquids produced intermediate mutagenic effects. Overall, none of the samples were found to be directly mutagenic for any Salmonella strain in the absence of rat liver homogenate. Variables influencing the relative mutagenicity of the fractions included ash content, temperature of the reactor, amount of hydrogen used, and pressure used in the vacuum distillation of the separator bottoms. (14 Refs)

43. ISOLATION OF A MUTAGEN PRODUCED IN THE HUMAN COLON BY BACTERIAL ACTION.

Wilkins TD, Lederman M, Van Tassell RL, Wattenberg LW, Wilkins TD, Bruce WR, Goldin BR
Dept. Anaerobic Microbiology, Virginia Polytechnic Inst. and State Univ., Blacksburg, VA, 24061
Banbury Rep; 7:205-214 1981

The feces of about 30% of North Americans contain mutagenic activity in the Ames assay, and greater than 90% of this mutagenicity is due to one substance. The isolation and purification of this substance are described. Evidence indicating its production by colonic bacteria is presented. Dietary supplementation with ascorbic acid or vitamin E (3 wk each) did not affect the fecal concentration of the mutagen in three donors. Two of these donors were a married couple who ate almost every meal together, but the wife consistently excreted much more mutagen than her husband. The daily variation in mutagen excretion was completely random. The mutagen was stable under strictly anaerobic conditions and strongly fluorescent under long-wave UV light. It was extremely sensitive to oxidation, decomposing (in a manner similar to catalytic lipid peroxidation) to a substance which was neither mutagenic nor fluorescent. The mutagen acted directly on Salmonella strains TA98 and TA100 in both its crude and purified forms. The presence of microsomal enzymes reduced its mutagenicity. Since the substance was not mutagenic for the parent strain of TA98 (TA1538), it may act by causing base-pair substitutions. This substance is not the only mutagenic compound present in human feces, but it is the most active substance in the Ames test. (10 Refs)

44. PROPERTIES OF A MUTAGEN ISOLATED FROM FECES.

Bruce WR, Varghese AJ, Land PC, Krepinsky JJ, Montesano R, Wilkins TD, Van Soest PJ, Goldin BR, Reddy BS, Kingstn DG, Tannenbaum ST, Balis E, Watson JD, Mower HF

Ontario Cancer Inst., Toronto, Ontario, M4X 1K9, Canada

Banbury Rep; 7:227-238 1981

A mutagen, with strong activity on Salmonella strain TA100 without metabolic activation, was detectable (greater than 200 revertants/g) in freeze-dried feces from 4/12 healthy subjects and 4/7 patients previously operated upon for rectal cancer who were not on medication at time of study. High mutagen levels (greater than 800 revertants/g) were detected in one normal subject and one cancer patient. Mutagenicity was strong correlated with UV absorption of the substance. The UV spectrum of the mutagen resembled that of a polyene antibiotic (filipin) but its nuclear magnetic resonance spectrum did not. The available data indicate at least two hydroxyl groups but no carboxyl or benzoyl groups in the molecule. (8 Refs)

45. FECAL MUTAGENS IN TWO JAPANESE POPULATIONS WITH DIFFERENT COLON CANCER RISKS.

Mower HF, Ichinotsubo D, Wang LW, Mandel M, Stemmermann G, Nomura A, Heilbrun L, Kamiyama S, Shimada A

Dept. Biochemistry and Biophysics, John A. Burns Sch. Medicine, Univ. Hawaii at Manoa, Honolulu, HI, 96822

Cancer Res; 42(3):1164-1169 1982

Human feces from 223 Japanese in Hawaii at high risk for colon cancer and feces from 166 Japanese of northern rural Japan at low risk for colon cancer were shown to contain mutagenic activity under five different test conditions. The first assay, using the Ames TA98 and TA100 Salmonella test, detected ether-soluble mutagens in the presence and absence of rat liver microsomes. Of these, the TA98 direct-acting mutagens are present more frequently in the feces of the high-risk population than the low-risk population at a high level of statistical significance (p less than 0.01). TA98 mutagens activated by rat liver microsomes also occur significantly more frequently in the feces of the Japanese from Hawaii (p less than 0.05). Mutagens detected by TA100 in the presence and absence of rat liver microsomes are not commonly found in either Japanese population. The second bacterial test system used to detect fecal mutagens uses Escherichia coli rec-. This system detects water-soluble fecal mutagens which are also present more frequently in the high-risk population than in the low-risk population (p less than 0.05). (Author abstract) (27 Refs)

46. THE USE OF BACTERIAL FLUCTUATION TESTS IN STUDIES OF MUTAGENIC ACTIVITY IN HUMAN FECES.

Venitt S, Pickering SP, Hill MJ, Fernandez F
Pollards Wood Res. Station, Chester Beatty Res. Inst., Inst. Cancer Res.: Royal Cancer Hosp., Chalfont St. Giles, Bucks, HP8 4SP, England
Banbury Rep; 7:239-245 1981

Fecal excretion of mutagenic substances was identified in 4/7 normal subjects with Salmonella typhimurium TA100 and Escherichia coli WP2uvrA(p) (a tryptophan-requiring strain). Metabolic activation was not required. High doses of the substances were toxic to the bacteria. The bacterial fluctuation test (method of Gatehouse and Delow) showed a significant dose-response relationship was present in each assay. This assay method can be used with any genetic system involving mutation for auxotrophy to nonleaky prototrophy. (8 Refs)

47. MUTAGENIC AND ALKYLATING ACTIVITIES OF 3-METHYL-1-PHENYLTRIAZENES AND THEIR POSSIBLE ROLE AS CARCINOGENIC METABOLITES OF THE PARENT DIMETHYL COMPOUNDS.

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Cancer Res; 42(4):1446-1453 1982

The compound 3-methyl-1-phenyltriazene and a series of ring-substituted derivatives (4-methylphenyl, 4-chlorophenyl, and 2,4,6-trichlorophenyl), structurally related benzenediazonium fluoborates and phenyl azides, as well as the recently isolated [1-methyl-3-(2,4,6-trichlorophenyl)-2-triazeno]methyl beta-D-glucopyranoside uronic acid, were studied for their mutagenic activity in Salmonella typhimurium strains. Of these compounds, the 3-methyl-1-phenyltriazene derivatives and 2,4,6-trichlorobenzenediazonium fluoborate were found to be direct-acting mutagens; the glucuronide was active in strain TA 1530 only after deconjugation with beta-glucuronidase. The half-lives of the monomethylphenyltriazenes in vitro were determined and compared with their methylating activity towards 4-(4-nitrobenzyl)pyridine and their mutagenicity. The results are discussed in relation to the possible mechanism of action of the N,N-dimethylphenyltriazenes and their monomethyl derivatives as mutagens and organ-specific carcinogens. (Author abstract) (43 Refs)

48. SISTER-CHROMATID EXCHANGE AND CHROMOSOMAL ABERRATIONS BY DHAQ AND RELATED ANTHRAQUINONE DERIVATIVES IN CHINESE HAMSTER OVARY CELLS.

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Dept. Pharmacology, Univ. Kansas Medical Center, Kansas City, KS, 66103
Mutat Res; 101(1):77-86 1982

Induction of sister-chromatid exchanges (SCE), chromosomal aberrations, and antiproliferative activity of DHAQ (a dihydroxy bis(aminoalkylamino)-substituted anthraquinone) and several related analogues were investigated in Chinese hamster ovary cells and the results compared with those of doxorubicin (DOX). Marked genotoxic effects were observed with DHAQ, DOX, and two analogues of DHAQ (compounds IIIc and IV), with the most potent effect observed with DHAQ. At 50 nanoM, DHAQ completely inhibited cells from entering second metaphase by the end of the 48-hr culture period; comparable effects were observed with 1,000 nanoM of the other compounds. At 1 nanoM, the frequency of SCE was similar between the agents, although DHAQ induced the most dramatic chromosomal aberrations. DHAQ induced a more potent genotoxic effect on the induction of chromosomal aberrations than on SCE induction. Compound IIIc enhanced SCE induction. DOX showed a linear dose response in its ability to induce chromosomal aberrations at concentrations of 10 and 200 nanoM; the SCE effect were not as obvious. Compounds IIIa, IIIb, and V significantly induced SCE; chromosomal aberrations were generally observed at lower concentrations than SCE. Antiproliferative effects of these agents were correlated with their genotoxic effects, with DHAQ having the most antiproliferative effect followed by DOX, compound IIIc, and compound IV; compound IIIb exhibited a significant effect only at 1,000 nanoM, while IIIa and V showed no antiproliferative effects. Genotoxic effects were always observed at lower concentrations than antiproliferative effects. (24 Refs)

49. SISTER CHROMATID EXCHANGES AND MUTAGENIC CARCINOGENS.

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Gann Monogr Cancer Res; 27:109-124 1982

Use of sister chromatid exchange (SCE) induction for detecting mutagenic effects in mammalian cells is reported. SCEs are produced with unrepaired lesions are present when the cell passed through S phase and chromosome replicated. Some chemical mutagens caused a 10-fold increase in background level of SCEs at concentrations of the chemical less than 1/100th of that required to induce ordinary chromosomal aberrations. Cultured Chinese hamster ovary cells with rat liver microsomes can be used to detect SCE induction. Suspected mutagens can be prescreened with the SCE test in sensitive mammalian cells by treating the cells in vitro with and without S-9 mix. Negative compounds should be tested in an in vivo test system to determine if the compounds can be activated under in vivo conditions. The SCE test was used to determine the following: which benzene metabolites were most likely responsible for the biologic effects, the stage of embryogenesis at which cells that are genetically capable of producing aryl hydrocarbon hydroxylase activated promutagens or procarcinogens, how long lesions induced by a short-lived proximate carcinogen last in cells of differing repair capacity, and whether mammalian cells exhibit novel DNA repair mechanisms. (58 Refs)

50. ASPERGILLUS NIDULANS: SYSTEMS AND RESULTS OF TESTS FOR INDUCTION OF MITOTIC SEGREGATION AND MUTATION. II. HAPLOID ASSAY SYSTEMS AND OVERALL RESPONSE OF ALL SYSTEMS. A REPORT OF THE U. S. EPA GENE-TOX PROGRAM.

Scott BR, Dorn GL, Kafer E, Stafford R
Phoenix, Lone Oak Lab., P.O. Box 744, Upton Road, Smithville, TX, 78957
Mutat Res; 98(1):49-94 1982

A critical evaluation of the 1965-1978 literature was made on the response of haploid Aspergillus systems to various agents, along with comparison to results obtained from in vivo carcinogenicity studies. Of the three test systems used, the methionine suppressor and 2-thioxanthine assays used multiallelic forward-mutations as a response to induced base-pair changes and small deletions, while the arginine system used reverse mutations of unspecified nature. Only 1 false positive hit, was found in comparison of the 27 chemicals (of 124 listed) with known in vivo results. Two of the 24 positive chemicals required metabolic activation (mammalian), and 5 were nonmutagenic for Salmonella. Most of the methionine and 2-thioxanthine systems used the Glasgow biAl; methG1 strain, while the arginine system used the BIN-252 strain. The suggested protocol emphasized complete removal of germination-inhibitory substance, notation of use of germinated or quiescent nuclei, adequate dose/time/response testing, metabolic activation, 8-methoxypsoralen with and without UV as positive and negative control, and, for the methionine system, mandatory spontaneous background mutation frequency assay. A statistical method of data treatment was applied involving survival fraction correlation with mutation frequency. An advantage of the 2-thioxoanthine over the methionine system was assignability of mutants to specific gene loci. (76 Refs)

51. THE INDUCTION OF MUTATION AND CELL DIFFERENTIATION BY CHEMICALS WHICH INITIATE OR PROMOTE TUMOR FORMATION.

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Gann Monogr Cancer Res; 27:127-144 1982

Detection of tumor promoting chemicals in mammalian cell culture systems is described. Chemical carcinogens are mutagenic for mammalian cells, with their degree of mutagenicity correlating with their degree of carcinogenicity. In some cases, the metabolites responsible for mutagenesis are also responsible for initiating the carcinogenic event. A cell/organ type specificity can be established with a cell-mediated assay. The effect of tumor promoters such as the phorbol-diesters in cultured human HO melanoma and human HL-60 promyelocytic leukemia cells was studied. In both HO and HL-60 cells, the ability of ten different phorbol esters to induce differentiation correlated with their tumor-promoting activity in mouse skin. Changes in polyamine levels may involve biological pathways other than the known biosynthetic ones and these pathways or their by-products may be involved in the control of cell growth and differentiation in HL-60 cells. Studies of specific binding of 20-[3H]-phorbol 12,13-dibutyrate (PDBu) in HL-60 cells demonstrated that down regulation of specific PDBu binding is an important phenomenon involved in the mechanism of action of phorbol esters and may lead to modification of various biological and biochemical events involved in cellular differentiation and perhaps tumor promotion. Human HO melanoma and HL-60 leukemia cells may be useful for studying the mode of action of known tumor promoters and in the identification of some unknown classes of tumor-promoting agents. (82 Refs)

BINDING OF CARCINOGENS AND THEIR METABOLITES TO MACROMOLECULES

52. ASSOCIATIONS OF BENZO[A]PYRENE WITH RAT-LIVER CHROMATIN AND THE CHROMATIN PROTEIN.

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Chem Biol Interact; 39(1):17-30 1982

Rat-liver nuclei were prepared in the course of time after the ip injection of [G-3H] benzo[a]pyrene ([3H]BP). The nuclei were lysed in the hypotonic buffer and centrifuged at 4000 x g. The recovery of the radioactivity of resulting supernatant (chromatin) was thus 91% at 24 hr, 68% at 48 hr and 74% at 168 hr after the ip injection. The incorporation into nucleosome-oligomer fraction was always much more than into those of monomer and DNA-rich fractions. The preferential incorporation was found in the fraction which was enriched in nonhistone chromatin proteins (NHCPs) of 49,000-55,000 daltons. This fraction steadily raised the incorporation level until at 168 hr after the ip injection. In contrast, the levels of histone and DNA fractions were always very low. The significant incorporation was observed in the fraction which was composed of five classes of histones and low mol wt NHCPs (less than 30,000 daltons), despite the very low incorporation into the histone fraction. The fluorographic analysis revealed the predominant incorporations at the positions of mol wt of 65,000, 52,000 and 44,000 daltons. In addition, the incorporations were clearly observed at the positions of 59,000, 49,000, 45,000, H1 histone, A24 protein and another one. On the other hand, these fractions were, at the final preparation steps, subjected to either dialysis or SDS-phenol treatment and/or acetone precipitation. The total recovery of radioactivity was thus 21% at 24 hr, 32% at 48 hr, and 52% at 168 hr after the ip injection. These results suggest that the chromatin contains considerable amounts of water-soluble, phenol and/or acetone-soluble BP-conjugates in the early period after the ip injection. (Author abstract) (37 Refs)

53. BINDING OF BENZO[A]PYRENE TO HISTONES AND ALTERED AFFINITY OF MODIFIED HISTONE 1 FOR DEOXYRIBONUCLEIC ACID.

Jenson JC, FitzGibbon J, Brennan LA, Litman GW
Walker Lab., Sloan-Kettering Inst., Rye, NY, 10580
Biochemistry; 21(4):601-607 1982

The covalent binding of benzo[a]pyrene (B[a]P) to acid-extractable chromosomal proteins and the subsequent effect on histone 1-DNA interaction have been characterized in a model system by utilizing calf thymus nuclei as targets and rat liver microsomes as an exogenous source of enzymes for the metabolic activation of B[a]P. A two-step ion-exchange chromatography and desalting procedure was employed for removing noncovalently bound B[a]P and other contaminants. Fluorography of acetic acid-urea and Triton-acetic acid-urea-polyacrylamide gels indicated that H1 and H3 were the only principal histone targets in [3H]B[a]P-modified calf thymus nuclei. The validity of this assignment was confirmed by comparison of the chromatographic distributions of [3H]B[a]P cpm among peptides derived from the HClO4-soluble (H1) and HClO4-insoluble (core histones) protein fractions to the distributions obtained for authentic individual histone fractions. Comparison of amino acid compositions in individual peptide fractions which bound [3H]B[a]P differentially yielded some insight into the probable target amino acid residues for B[a]P binding. On the basis of electrophoresis in polyacrylamide gels, it appeared as if B[a]P had bound to multiple subfractions of Hl and H3. The equivalent distribution of covalently attached [3H]B[a]P among the major peptides of H1 and H3 modified either in intact nuclei or while free in solution implied that the relative accessibility of major portions of the H1 and H3 molecules for covalent B[a]P binding is not affected by interactions with DNA or other chromosomal proteins. Covalent attachment of [3H]B[a]P to purified H1 reduced the affinity of this histone for DNA-cellulose (Author abstract) (55 Refs)

54. INFLUENCE OF COENZYME A ON THE IN VITRO BINDING OF BENZO(A)PYRENE METABOLITES TO PROTEIN.

Raha CR, Gallagher CH, Reeve VE
Eppley Inst. Res. in Cancer and Allied Diseases, Univ. Nebraska Medical Center, 42nd and Dewey Ave., Omaha, NE, 68105
Res Commun Chem Pathol Pharmacol; 35(2):329-332 1982

Incubation of 20,000 x g supernatants of liver homogenates from female Wistar rats with benzo(a)pyrene (BP) and other cofactors in the presence of coenzyme A (CoA) produced metabolites that required extensive hydrolysis successively in 2N NaOH, 2N HCl, 2N NaOH and 6N HCl for their release. It is suggested that coenzyme A activated benzpyrenyl amino acid formed via epoxide(s). The activated amino acid(s) became bound to thiol protein. (Author abstract) (6 Refs)

55. EXCISION OF BENZO[A]PYRENE DIOL EPOXIDE I ADDUCTS FROM NUCLEOSOMAL DNA OF CONFLUENT NORMAL HUMAN FIBROBLASTS.

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Chem Biol Interact; 38(3):261-274 1982

The formation and removal of covalent adducts of racemic 7beta,8alpha-dihydroxy-9alpha,10alpha-epoxy-7,8,9,10 tetrahydrobenzo[a]pyrene (BPDE I) was studied in nucleosomal DNA of confluent cultures of normal human fibroblasts (NF). For this purpose NF were prelabeled in their DNA with [14C]-thymidine and treated with [3H]BPDE I. The adducts were composed of 77% (7R)-N2-(7beta,8alpha,9alpha-trihydroxy-7,8,9,10 tetrahydrobenzo[a]pyrene-10-yl)deoxyguanosine, 12% of the corresponding 7S-enantiomer and of minor amounts of adducts to cytosine and adenine. The adduct composition did not change significantly in 24-hr post treatment incubation. Bulk mononucleosomes were prepared from micrococcal nuclease digested nuclei and their DNA analyzed by gel electrophoresis. The adduct concentrations were determined in 145 base pair (bp) nucleosomal core-DNA, 165 bp chromatosomal DNA and in total nuclear DNA. From these data the concentration in nucleosomal linker-DNA was calculated. The initial adduct distribution was non-random and 6.3 times higher in 47 bp linker-DNA relative to 145 bp core-DNA and 9.2 times higher in 27 bp linker-DNA relative to 165 bp chromatosomal DNA. Adduct removal was very rapid during the first 8 hr and more efficient from linker-DNA than from core-DNA. After this early phase the adducts located in 145 bp core-DNA became refractory to further excision and represent a major fraction of the adducts persisting in DNA of NF over a prolonged period. In contrast, further adduct removal was observed from nucleosomal linker-DNA. (Author abstract) (31 Refs)

56. EFFECT OF BUTYLATED HYDROXYANISOLE, ALPHA-ANGELICA LACTONE, AND BETA-NAPHTHOFLAV ONE ON BENZO(A)PYRENE:DNA ADDUCT FORMATION IN VIVO IN THE FORESTOMACH, LUNG, AND LIVER OF MICE.

Ioannou YM, Wilson AG, Anderson MW
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Cancer Res; 42(4):1199-1204 1982

The effects of alpha-angelica lactone (alpha-AL), butylated hydroxyanisole (BHA), and beta-naphthoflavone (beta-NF) on the amount of benzo(a)pyrene (BP) metabolite:DNA adducts formed in the forestomach, lung, and liver of ICR/Ha mice were investigated 48 hr after po administration of BP. BP was administered to mice in amounts known to result in BP-induced neoplasia in certain tissues. Analysis of deoxyribonucleosides by high-pressure liquid chromatography showed that several BP metabolite:DNA adducts were formed in each tissue examined. The major identified adduct in each tissue cochromatographed with the (-)-7beta,8alpha-dihydroxy-9alpha,10alpha-epoxy 7,8,9,10-tetrahydrobenzo(a)pyrene (BPDEI)-deoxyguanosine adduct. The (-)-7beta,8alpha-dihydroxy-9beta,10beta epoxy-7,8,9,10 tetrahydrobenzo(a)pyrene (BPDEII):deoxyguanosine adduct was detected in each of the tissues. As a percentage of total DNA-associated radioactivity, the BPDEI:DNA and BPDEII:DNA adducts accounted for 14% in the forestomach, 39% in the lung, and 3% in the liver. Another adduct, possibly derived from BP: phenol(s), was detected in lung and liver. Early eluting unidentified DNA-associated radioactivity was also present in each of the tissues and accounted for the majority of the radioactivity (88% in forestomach, 57% in lung, and 97% in liver). Although total DNA-associated radioactivity in liver was approximately 15-fold higher than in lung and 5-fold higher than in forestomach, the specific activities of the BPDEI:adducts and of the BPDEII:adducts were approximately the same in these organs. Addition of alpha-AL or BHA to the diet inhibited BPDEI:DNA adduct formation in the forestomach and liver but not in the lung. The effect of beta-NF was not tissue specific; this aryl hydrocarbon hydroxylase inducer decreased markedly (80 to 90%) BPDEI:DNA adduct formation in all three tissues. The radioactivity associated with the early eluting peaks was also reduced when alpha-AL, BHA, or beta-NF was fed to the mice. The inhibition of BPDEI:DNA and BPDEII:DNA adduct formation by alpha-AL, BHA, and beta-NF is discussed in relation to similar studies where these compounds inhibited BP-induced neoplasia. (Author abstract) (53 Refs)

57. EFFECTS OF POLYCHLORINATED BIPHENYLS AND ENVIRONMENTAL TEMPERATURE ON IN VITRO FORMATION OF BENZO[A]PYRENE METABOLITES BY LIVER OF TROUT (SALMO GAIRDNERI).

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Biochem Pharmacol; 31(4):561-566 1982

Rainbow trout (Salmo gairdneri) held at 7 C and 16 C were given Aroclor 1254 (PCB) (10 mg/kg body wt) via ip injections. The binding of [3H] benzo[a]pyrene (BaP) to deproteinized salmon sperm DNA was assayed (pmoles BaP equivalents per mg DNA per mg protein) using the post-mitochondrial supernatant (S 10) fractions from livers of fish at 24-168 hr after the PCB exposure. Liver enzymes from the untreated fish acclimated at 7 C yielded an av binding value (0.37 -0.17) which was significantly greater (p less than 0.05) than the value (0.07 -0.03) for untreated fish at 16 C. Liver supernatant fractions from PCB-induced fish acclimated at 16 C and sampled at 24-120 hr showed a substantial increase (p less than 0.05) in the binding (av value 2.4 -1.8) compared to the value obtained with untreated fish at 16 C. At 24, 48 and 120 hr after the PCB treatment of fish held at 7 C, there was no significant increase in the binding value or extent of metabolism of BaP compared to that obtained with the untreated fish at 7 C. However, at 168 hr, three of four fish at 7 C responded to the PCB treatment with significantly (p less than 0.05) increased binding values (3.3 -1.6). Chromatographic analyses of the ethyl acetate-soluble metabolites revealed that 3-hydroxy BaP and 7,8- and 9,10-dihydrodiols were the major metabolites; K-region metabolites were formed in trace amounts in untreated and PCB-treated fish at both temperatures. No marked qualitative differences were observed in metabolite profiles after the PCB treatment; however, overall metabolism of BaP and production of reactive metabolites by liver enzymes were considerably (p less than 0.05) enhanced in the PCB-induced fish at both 7 C and 16 C. (Author abstract) (42 Refs)

58. COMPARISON OF BENZO(A)PYRENE METABOLISM IN BRONCHUS, ESOPHAGUS, COLON, AND DUODENUM FROM THE SAME INDIVIDUAL.

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Cancer Res; 42(3):934-938 1982

The metabolism of benzo(a)pyrene has been investigated in cultured normal human bronchus, colon, duodenum, and esophagus obtained from the same patient. The highest total metabolism was found in bronchus and duodenum, while the highest mean binding level was observed in the bronchus followed, in order, by the esophagus, duodenum, and transverse colon. A 30-fold interindividual variation in the binding level was found in each of the four organs studied, and a positive correlation between the binding levels in bronchus, colon, and duodenum was found. In human bronchus, a positive correlation was found between level of binding of benzo(a)pyrene to DNA and the amount of both benzo(a)pyrene 7,8-diol and the combined group of 3-hydroxybenzo(a)pyrene, benzo(a)pyrene 9,10-diol, and water-soluble metabolites . A significantly higher relative amount of benzo(a)pyrene tetrols and benzo(a)pyrene 9,10-diol was found by human bronchus compared to the gastrointestinal tissues. while a higher level of benzo(a)pyrene was formed by the latter. The relative distribution of benzo(a)pyrene-DNA adducts was similar in all four organs, the major DNA adduct being formed by trans-addition of anti-7,8-dihydroxy-9,10-epoxide-7,3,9, 10-tetrahydrobenzo(a)pyrene to the 2-amino group at guanine. These results indicate that the metabolism of benzo(a)pyrene by at least four different organs is qualitatively similar but that quantitative differences exist. (Author abstract) (46 Refs)

59. EFFECTS OF ESTROGENS ON ARYL HYDROCARBON HYDROXYLASE MEDIATED BINDING OF BENZO(A)PYRENE METABOLITES TO DNA IN VITRO.

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Biochem Biophys Res Commun; 104(4):1349-1355 1982

Liver microsomes from mice injected with 0.1 or 2 mg of estradiol (ES) 24 prior to, during and 24 hr after injection of 3-methylcholanthrene (MC), exhibited a significantly decreased capacity to mediate the binding of benzo(a)pyrene metabolites to DNA. compared to microsomes from mice which received only MC. The enzyme and cytochrome components of the aryl hydrocarbon hydroxylase (AHH) were not affected by either ES treatment, suggesting ES may act as a non-competitive inhibitor of AHH activity. (20 Refs)

60. METABOLISM OF POLYCYCLIC AROMATIC HYDROCARBONS AND COVALENT BINDING OF METABOLITES TO PROTEIN IN RAT ADRENAL GLAND.

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Cancer Res; 42(4):1479-1486 1982

The metabolism of the carcinogenic and adrenocorticolytic polycyclic aromatic hydrocarbon 7,12-dimethylbenz(a)anthracene in rat adrenals was investigated. Both 7,12-dimethylbenz(a)anthracene and benzo(a)pyrene, which also is a well-known carcinogen but has no short-term effects on rat adrenals, appear to be metabolized by one common type of cytochrome P-450-dependent monooxygenase localized in the endoplasmic reticulum. Studies of the kinetic properties of this cytochrome P-450 reveal that the Km values for 7,12-dimethylbenz(a)anthracene and benzo(a)pyrene are lower than 3 uM. Identification of metabolites indicates that, with both 7,12-dimethylbenz(a)anthracene and benzo(a)pyrene, phenols and diols were formed the relative rates of formation of which were markedly influenced by the epoxides hydrase inhibitor cyclohexane oxide, suggesting that epoxides are intermediate metabolites. Added or endogenous microsomal glutathione S-transferase B had little or no effect on the distribution of metabolites. A rather selective binding of metabolites of 7,12-dimethylbenz(a)anthracene to soluble and microsom al proteins was demonstrated. The adrenal cytochrome P-450 involved in the conversion of these polycyclic aromatic hydrocarbons appears to be unrelated to those responsible for the synthesis of mineralocorticoids and glucocorticoids from cholesterol. Among androgens and estrogens, estradiol proved to be the most inhibitory steroid, suggesting a role of the hydrocarbon-metabolizing cytochrome P-450 in estrogen biosynthesis. However, no such function could be demonstrated conclusively. The metabolite patterns and the effects of nonsteroid inhibitors of liver monooxygenases, eg, alpha-naphthoflavone, SU 9055, and ellipticine, suggest that the properties of this cytochrome P-450 resemble those of the 3-methyl-cholanthrene-inducible cytochrome P-488 from rat liver. (Author abstract) (58 Refs)

61. DNA METHYLATION LEVELS IN NORMAL AND CHEMICALLY-TRANSFORMED MOUSE 3T3 CELLS.

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Biochem Biophys Res Commun; 104(4):1489-1494 1982

Normal mouse embryo 3T3 cells grown in culture and cells transformed by benzo(a)pyrene and methylcholanthrene were analyzed by high performance liquid chromatography (HPLC) to determine the 5-methylcytosine to cytosine base ratios in their total genomic DNA. The DNA methylation levels were approx equal in the three cell lines. Findings obtained with HPLC and those obtained by other techniques are discussed. (16 Refs)

62. RAPID RELEASE OF CARCINOGEN-GUANINE ADDUCTS FROM DNA AFTER REACTION WITH N-ACETOXY-2-ACETYLAMINOFLUORENE OR N-BENZOYLOXY-N-METHYL-4-AMINOAZOBENZENE.

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McArdle Lab. Cancer Res., Univ. Wisconsin Medical Sch., Madison, WI, 53706
Carcinogenesis; 3(1):81-88 1982

Reaction of N-benzoyloxy-N-methyl-4-aminoazobenzene (N-benzoyloxy-MAB) or N-acetoxy-N-acetyl-2-aminofluorene (N-acetoxy-AAF), model ultimate aromatic amine or amide carcinogens, with [purine-14C]DNA at pH 7.4 or reaction of N-hydroxy-2-aminofluorene (N-hydroxy-AF) at pH 4.6 resulted in the rapid release of 14C-containing products not precipitable with the DNA. Four such products were obtained on reaction with N-acetoxy-AAF, two with N-hydroxy-AF, and six with N-benzoyloxy-MAB. Depending on the DNA sample used, the total amounts of 14C in these products from the reactions with N-benzoyloxy-MAB or N-acetoxy-AAF ranged from about 5% to as much as 30-40% of the amounts in the N-(deoxyguanosin-8-yl)-MAB or N-(deoxyguanosin-8-yl)-AAF residues in the DNA from the same reaction mixtures. Reactions with N-acetoxy-[acetyl-3H]AAF showed that the two major products retained the amide residue from the N-acetoxy-AAF. when the reactions were carried out with [guanine-(8-3H; 8-14C); adenine-(2,8-3H; 8-14C)]DNA, the two major products formed from N-acetoxy-AAF and four products formed from N-benzoyloxy-MAB had very low 3H:14C ratios; these ratios were those expected for guanine derivatives which had lost the 8-3H. Studies on the major DNA adducts N-(deoxyguanosin-8-yl)-MAB and N-(deoxyguanosin-8-yl)-AAF indicated that the new adducts were not formed from these nucleosides. The data suggest that the two major AAF products and the four MAB adducts studied are guanine derivatives formed by depurination of N-7 substituted adducts in the DNA. (Author abstract) (49 Refs)

63. FORMATION AND REMOVAL OF (GUAN-8-YL)-DNA-2-ACETYLAMINOFLUORENE ADDUCTS IN LIVER AND KIDNEY OF MALE RATS GIVEN DIETARY 2-ACETYLAMINOFLUORENE.

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Cancer Res; 42(4):1317-1321 1982

Radioimmunoassay has been used to measure acetylated and deacetylated deoxyguanosine C-8 DNA adducts of 2-acetylaminofluorene in liver and kidney DNA of male Wistar-Furth rats fed a dietary regimen of 0.02 or 0.04% 2-acetylaminofluorene. When adduct formation was monitored during continuous feeding up to 60 days, substantial levels of binding (80 fmol/ug DNA) were observed in liver by 1 day, and maximum steady-state values averaging 230 fmol/ug DNA were reached by 30 days. Initially, during the continuous feeding, about 80% of the total C-8 adducts were deacetylated [N-deoxyguanosin(8-yl)aminofluorene] and this proportion increased to about 97% by 15 and 30 days of administration of 0.04 and 0.02% 2-acetylaminofluorene diets, respectively. Levels of C-8 adducts bound to kidney DNA in the same animals averaged 10 to 15% of the liver values with greater than or equal to 80% of these adducts in the deacetylated form. In separate experiments, rats were exposed to 2-acetylaminofluorene for 3, 7, 28, and 112 days; the carcinogen-containing diet was discontinued; and C-8 adducts were monitored during 1, 7, and 28 days of feeding control diet. At both carcinogen doses, after dietary administration for 3 or 7 days, there was a rapid decrease in liver C-8 adducts so that, after 28 days on control diet, 65 to 90% of the original adducts were no longer present in the DNA. In contrast, in animals fed 0.02% 2-acetylaminofluorescene for 28 days, there were high levels (70 to 100% of the original C-8 adduct) remaining on the DNA at the end of 28 days on control diet. This apparent loss in capacity for removal of C-8 adducts is discussed in relation to biological and biochemical changes induced in the rat liver during 2-acetylaminofluorene hepatocarcinogenesis. (Author abstract) (26 Refs)

64. METABOLISM OF N-NITROSAMINES BY CULTURED HUMAN AND RAT ESOPHAGUS.

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Cancer Res; 42(4):1307-1311 1982

The metabolism of several N-nitrosamines (N-nitrosodimethylamine, N-nitrosoethyl methylamine, N-nitrosodiethylamine, N-nitrosobenzylmethylamine, and N-nitrosopyrrolidine) in cultured human and rat esophagus has been investigated by measuring CO2, metabolites with an oxo group and metabolites bound to DNA. Both acyclic and cyclic N-nitrosoamines were metabolized by rat esophagus. The highest level of metabolite binding was seen with N-nitrosobenzylmethylamine, an organotropic carcinogen for the rat esophagus. The binding level was about 100-fold higher than in human esophagus. This compound methylated rat esophageal DNA at positions 7 and O6 of guanine. The level of benzylation in rat was one-tenth the level of methylation. Formation of benzaldehyde exceeded that of formaldehyde plus CO2 by a factor of 6, indicating that the methylene group was preferentially oxidized. N-Nitrosoethylmethylamine was preferentially oxidized by rat esophagus in the ethyl group. The highest binding level to DNA from this compound was observed with the methyl group. No binding was detected to human esophagus. N-Nitrosopyrolidine was oxidized by both rat and human esophagus in the alpha position, as measured by the formation of 2,4-dinitrophenylhydrazone derivative of 4-hydroxybutanal. Binding of metabolites of N-nitrosopyrrolidine to DNA was detected only in rat esophagus. As measured by the formation of both CO2 and formaldehyde, N-nitrosodimethylamine was metabolized by both human and rat esophagus. While most of the radioactivity associated with DNA was found to be incorporated into guanine and adenine, methylation of the guanine positions 7 and O6 was detected by chromatography of the hydrolyzed rat DNA. The results indicate significant quantitative and perhaps qualitative differences between cultured rat and human esophagus in their ability to activate N-nitrosamines, although unknown physiological differences after culture may contribute to this difference. (44 Refs)

65. A FREE RADICAL MECHANISM FOR ARYLAMINE INDUCED CARCINOGENESIS INVOLVING PEROXIDES.

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Biochem Pharmacol; 31(4):607-608 1982

A 1 e oxidation of N-methyl-4-aminoazobenzene (MAB) catalyzes more binding than the 2 e monooxygenase mechanism in the presence of liver sulfotransferase. Covalent binding of (14C)MAB metabolites to exogenous DNA or microsomal protein demonstrated that hydroperoxide was almost 400x more effective than NADPH in catalyzing the binding.

NADPH/reductase may reduce the radical formed by the 1 e oxidation pathway of cytochrome P450. The hydroperoxide catalyzed binding was not affected by addition of cytosol, while the NADPH system was markedly enhanced. Addition of ATP and sulfate further enhanced the cytosol effect, suggesting that the cytosol effect was probably due to sulfotransferase acting on the NOH M AB formed by the 2 e oxidation pathway carried out by microsomal amine oxidase/4. No NOH MAB was formed with hydroperoxide. Cytochrome P450 catalyzed both N demethylation and ring hydroxylation of MAB and the N hydroxylation was catalyzed by microsomal amine oxidase. In dogs and mice, the 1 e pathway of the monooxygenase activity of bladder and lung tissue may be responsible for carcinogenesis in these organs following administration of p-dimethylaminoazobenzene. In mouse liver carcinogenesis, both the 1 e and 2 e pathways should be considered. (9 Refs)

66. XANTHINE OXIDASE CATALYZED BINDING OF 1-NITROPYRENE TO DNA.

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Biochem Biophys Res Commun; 104(2):727-732 1981

Incubation of (4,5,9,10-3H)1-nitropyrene (1-NP: 20uM) with 2 mg/ml calf thymus DNA, xanthine oxidase (XO: 0.5 U/ml), and hypoxanthine (HX: 3.7 milliM) resulted in XO and HX becoming covalently bound to the DNA. The binding was linear for approx 30 min and reached a plateau at 120 min, with an estimated final binding level of 200-250 adducts/10(6) nucleotides. Adduct formation increased as enzyme concentration increased; it decreased in a concentration-dependent manner in response to the specific XO inhibitor allopurinol. Nitroreduction of 1-NP yields a species which readily reacts with DNA; the activity may be the basis of the compound's observed mutagenicity in bacteria. (23 Refs)

67. REACTIONS OF VINYL CHLORIDE WITH RNA AND DNA OF VARIOUS MOUSE TISSUES IN VIVO.

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Arch Toxicol; 49(2):117-129 1982

The irreversible binding of 14C-vinyl chloride metabolites to RNA and DNA of mouse brain, lung, liver, kidney, spleen, pancreas, and testes after a single ip injection has been studied. Hydrolysates of nucleic acids from selected organs were separated on Aminex A6 for quantitation of alkylation products. Radioactivity in nucleic acids was registered in all of the studied organs with the exception of brain. RNA from spleen, pancreas and liver, and DNA from spleen and liver contained the highest amounts of radioactivity. In nucleic acids from spleen and pancreas, both organs of high metabolic activity, the entire radioactivity was found metabolically incorporated as C1-fragments. In RNA of kidney and liver, a large part of the radioactivity was also present as incorporated C1-fragments, but 3,N4-ethenocytidine (in kidney) as well as 1,N6-ethenoadenosine and 1,N6-ethenoadenine (in kidney and liver) were identified as alkylation products. In liver DNA, incorporation of C1-fragments was insignificant, indicating different interactions of vinyl chloride metabolites (C1-fragments and alkylating products) with RNA and DNA. The elution profiles of radioactivity in hydrolysates of liver DNA were dominated by an alkylation product of unknown structure (probably a derivative of deoxyguanosine). Possibly, 1,N6-ethenodeoxyadenosine and 1,N6-ethenoadenine were also present in liver DNA. The results are consistent with the ability of viny chloride to act as a multipotent carcinogen by alkylation of DNA in several tissues. (Author abstract) (45 Refs)

68. COVALENT BINDING OF CARBON TETRACHLORIDE METABOLITES TO THE HEME MOIETY OF CYTOCHROME P-450 AND ITS DEGRADATION PRODUCTS.

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Res Commun Chem Pathol Pharmacol; 35(2):283-290 1982

Trichloromethyl free radicals (CCl3*) produced during a benzoyl peroxide decomposition of CCl4 covalently bind to hemin. Enzymatically produced CCl3* by an NADPH anaerobic liver microsomal activation of CCl4, covalently binds to heme and heme degradation products from CO-binding particles. 14C from CCl4 covalently binds to heme and heme degradation products from liver CO-binding particles from rats treated with 14CCl4. In vivo covalent binding of 14CCl4 reactive metabolites to proteins from CO-binding particles is higher than that to the whole microsomal proteins. The possible correlation between binding of CCl3 to heme and protein moieties of P-450 and CCl4 induced P-450 destruction is discussed. (Author abstract) (17 Refs)

69. SOLUBILIZATION OF THE CARCINOGEN NICKEL SUBSULFIDE AND ITS INTERACTION WITH DEOXYRIBONUCLEIC ACID AND PROTEIN.

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Biochemistry; 21(4):771-778 1982

Significant concentrations (1-10 mM) of nickel(II) were found in soln after incubation of the potent carcinogen nickel subsulfide in 0.05 M Tris-HCl, pH 7.4, solutions containing DNA, rat liver microsomes, and NADPH. The presence of NADPH decreased the rate of solubilization of nickel subsulfide. The solubilized nickel exhibited electronic absorption spectra and magnetic moments characteristic of octahedral nickel(II). The solubilized nickel(II) bound to DNA with an apparent equilibrium constant of 730 M-1 and with a saturation binding value of one nickel per 2.4 nucleotides. Microsomes lowered the saturation binding of nickel to DNA but dramatically increased the amount of nickel-DNA complex stable to precipitation with salt and poly-(ethylene glycol). The amount of protein associated with DNA precipitated from protein-extracted solutions correlated with the amount of nickel bound to DNA. These results suggest that microsomes mediate the binding of nickel to DNA by forming a stable ternary protein-nickel(II)-DNA complex. (Author abstract) (60 Refs)

ALTERATION OF MIXED FUNCTION OXIDASES BY CARCINOGENS

70. INDUCTION OF NEONATAL RAT SKIN AND LIVER ARYL HYDROCARBON HYDROXYLASE BY COAL TAR AND ITS CONSTITUENTS.

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J Invest Dermatol; 78(3):227-229 1982

Topical application of coal tar solution (USP) to neonatal rats resulted in the induction of skin and liver aryl hydrocarbon hydroxylase (AHH) activities. Furthermore indirect exposure of the animals to coal tar vapors resulted in induction of the enzyme in skin and liver. Cutaneous application of coal tar to pregnant rats resulted in induction of skin and liver AHH activity in both mothers and prenatal rats. Among several defined constituents of coal tar tested benzo(a)pyrene (BP), anthracene and acridine were found to have measurable induction effects on neonatal rat skin and liver AHH. These studies indicate that therapeutic coal tar solution as well as selected defined chemical constituents of coal tar are capable of altering the activity of AHH in skin and liver. (Author abstract) (25 Refs)

71. HYDROCARBON-BASED OILS AS INDUCERS OF CUTANEOUS ARYL HYDROCARBON HYDROXYLASE.

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Toxicol Lett; 10(2):213-217 1982

Modulation of drug-metabolizing mixed-function oxidase activity in the skin of rats by various petroleum mixtures was investigated. Skin application of Aroclor 1254 caused a 10-fold induction of benzo(a)pyrene (BAP) 3-hydroxylase activity and a 6 fold increase in diphenyloxazole (PPO) hydroxylase activity. Kuwait crude, used crankcase oil, and Fuel Oil NO. 2 applied to the skin also induced BAP hydroxylase and PPO hydroxylase to a lesser degree. Ip administration of Kuwait crude and used crank-case oil induced both hepatic BAP 3-hydroxylase and PPO hydroxylase activity. Cytochrome P 450 might play a significant role in the biotransformation of various chemicals and dermatologic medications. (9 Refs)

72. DIFFERENTIAL INDUCTION OF RAT HEPATIC CYTOCHROME P-448 AND GLUTATHIONE S-TRANSFERASE B MESSENGER RNAS BY 3-METHYLCHOLANTHRENE.

Pickett CB, Telakowski-Hopkins CA, Donohue AM, Lu AY, Hales BF
Dept. Biochemical Regulation, Merck Sharp and Dohme Res. Lab., Rahway, NJ, 07065
Biochem Biophys Res Commun; 104(2):611-619 1981

The in vitro levels of functional rat liver cytochrome P-448 and glutathione S-transferase B messenger(m)RNAs in response to 3-methylcholanthrene (3-MC) were quantitated by polyadenylate-RNA translation and specific immunoprecipitation with rabbit anti-cytochrome P-448 IgG. Administration of 40 mg/kg 3-MC to rats resulted in an accumulation of functional mRNAs specific for cytochrome P-448 and glutathione S-transferase B; 3-MC administration lowered rat serum albumin mRNA. Fluorograms of sodium dodecyl sulfate polyacrylamide gel electrophoresis revealed selective immunoprecipitation of two polypeptides of mol wt 55,000 and 54,000 daltons, respectively, from the in vitro translation system programmed with total liver polyadenylated-RNA from 3-MC-treated rats. No such polypeptides were precipitated from the translation system of untreated rats. Similar analysis revealed two primary translation products of glutathione S-transferase B, of 29,000 and 27,000 dalton mol wt, which were markedly more concentrated in the translation mixtures from 3-MC-treated rats. The elevation of immunoreactive cytochrome P-448 and glutathione S-transferase B after 3-MC treatment can be totally accounted for by increases in the level of mRNA coding the proteins. (18 Refs)

73. ONTOGENETIC VARIATION IN RAT LIVER, LUNG AND KIDNEY MONOOXYGENASE INDUCTION BY LOW DOSES OF BENZO(A)PYRENE AND CIGARETTE-SMOKE CONDENSATE.

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Br J Cancer; 44(6):902-910 1981

The specific lung-AHH induction, which we previously observed after the inhalation of cigarette smoke, is not due to the route followed by the inhaled smoke, for the same phenomenon occurs after ip injection of either cigarette smoke condensate (CSC) or benzo(a)pyrene in low doses. In this respect lung AHH behaves completely differently from the liver and kidney enzyme, in which organs, basal AHH activity (which is low in the fetus) increases rapidly after birth to reach the adult level 2 mo later, and is only inducible by CSC and low doses of BP in unweaned rats. In the lung, the basal AHH activity (low in the fetus) increases abruptly at birth, peaks in 5-day-old rats and then decreases slightly. Contrary to enzyme activity in other tissues, lung AHH cannot be induced in unweaned young animals. The enzyme subsequently becomes sensitive to inducing agents and is highly inducible in 90-day-old rats. Similar behavior occurs in two other enzymes linked to cytochrome P1450: ethoxycoumarin deethylase and ethoxyresorufin deethylase. The results could be related to the particular susceptibility of the lung to develop cancer after the inhalation of cigarette smoke. (Author abstract) (38 Refs)

74. EVIDENCE FOR A CYTOCHROME P-420 CATALYZED MECHANISM OF ACTIVATION OF N-HYDROXY-2-ACETYLAMINOFLUORENE.

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Cancer Biochem Biophys; 5(4):213-217 1981

Cytochromes P-450 and P-420 were solubilized from microsomes from perfused livers of phenobarbital-treated male rats. Electron spin resonance spectroscopy revealed the formation of a nitroxyl radical intermediate in the reaction activating N-hydroxy-2-acetylaminofluorene (N-OH-AAF) in the presence of linoleic acid hydroperoxide. The studies suggest the involvement of the P-450 system in conversion of N-OH-AAF to N-acetoxy-2-acetylaminofluorene and 2-nitrosofluorene, and confirm that the P-420 system, whether naturally occurring in microsomes or induced to form P-420 spin forms, is capable of catalyzing peroxidative type reactions. (18 Refs)

75. N-HYDROXYLATION ENZYMES OF CARCINOGENIC AMINOAZO DYES: POSSIBLE INVOLVEMENT OF CYTOCHROME P-448.

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Gan: 73(1):55-62 1982

N-Hydroxylation reactions of 3'-methyl-N,N-dimethyl-4-aminoazobenzene (3'-Me-DAB) and 3'-methyl-N-methyl-4-aminoazobenzene (3'-Me-MAB) were studied by measuring the nitroxide radical generated from N-hydroxylated products of these aminoazo compounds. N-Hydroxylation activity was remarkably high in the microsomes from 3-methylcholanthrene (3-MC)-treated rats, whereas phenobarbital (PB) treatment had a slightly enhancing effect on the N-hydroxylation of 3'-Me-DAB and a rather inhibitory effect on that of 3'-Me-MAB. Either NADPH or NADH was effective for the N-hydroxylation of 3'-Me-MAB, though the former was slightly more effective. For the reaction of 3'-Me-DAB the effect of NADPH and NADH was additive, but this was not the case for 3'-Me-MAB. Carbon monoxide, metyrapone and 2-dimethylaminoethyl-2,2-diethylvalerate hydrochloride (SKF-525A), inhibitors of cytochrome P-450, had no inhibitory effect on the N-hydroxylation of 3'-Me-DAB and 3'-Me-MAB. On the other hand, alpha-naphthoflavone, an inhibitor of cytochrome P-448, considerably inhibited the N-hydroxylation of these aminoazo dyes. In the case of partially purified mixed function amine oxidase (MFAO), 1-(1-naphthyl)-2-thiourea, an inhibitor of MFAO, completely inhibited the N-hydroxylation of 3'-Me-MAB as well as the N-oxidation of dimethylaniline. On the other hand, in a microsomal system the inhibition of the N-hydroxylation was at most 40% at the concentration giving complete inhibition of the N-oxidation of dimethylaniline. From these results, it is concluded that, in addition to MFAO, cytochrome P-448 is involved in the N-hydroxylation of MAB. (Author abstract) (26 Refs)

76. THE DAMAGE OF THE HEPATIC MIXED FUNCTIONAL OXYGENASE SYSTEM BY CCL4: SIGNIFICANCE OF INCORPORATION OF 14CCL4 METABOLITES IN VIVO.

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Exp Mol Pathol; 36(1):34-43 1982

The relation between incorporation of 14C from 14CCl4 into liver lipids and damage to the mixed functional oxygenase system of liver microsomes was investigated in rats of different sex o r differently pretreated. Under the respective conditions of pretreatment the 14C incorporation rate and the relative decrease of the cytochrome P-450 level as the parameters most influenced by CCl4 were compared with those for untreated female rats. Induction by 3-methylcholanthrene does not alter both parameters. Induction by sodium phenobarbital enhances the 14C incorporation rate as well as the cytochrome P-450 decrease but the latter is more affected. In male rats only the 14C incorporation rate increased. Vitamin D3-pretreated rats showed a smaller decrease of cytochrome P-450 but an enhanced 14C incorporation rate. Therefore, there is no correlation between the cytochrome P-450 decrease and 14C incorporation rate. Reasons for the lack of that correlation are discussed with regard to the mechanism of liver cell damage by carbon tetrachloride. (Author abstract) (55 Refs)

77. EFFECTS OF DIETARY AROCLOR 1254 AND CYCLOPROPENE FATTY ACIDS ON HEPATIC ENZYMES IN RAINBOW TROUT.

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Arch Environ Contam Toxicol; 11(1):87-91 1982

Combined effects of Aroclor 1254 (PCB) and cyclopropene fatty acids (CPFA) on various hepatic microsomal enzyme activities were determined in rainbow trout during a 15-wk feeding period. The hepatic microsomal enzyme inducing ability of the PCB was more than enough to overcome the mixed function oxidase suppressing activity of the CPFA. Given alone, the PCB increased cytochrome P-450; the effect was maximal by wk 5. The enzymes assayed were ethoxyresorufin-O-deethylase, ethyoxycoumarin-O-deethylase, and benzo(a)pyrene monooxygenase. (28 Refs)

78. EXPRESSION OF AROMATIC POLYCYCLIC HYDROCARBON-INDUCED MONOOXYGENASE (ARYL HYDROCARBON HYDROXYLASE) IN MAN X MOUSE HYBRIDS IS ASSOCIATED WITH HUMAN CHROMOSOME 2.

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Hum Genet; 59(4):277-280 1981

Mouse (BALB/cd) RAG cells, an established heteroploid cell line derived from renal adenocarcinoma, were fused with human fibroblast cell lines. Polycyclic aromatic hydrocarbon (PAH)-inducible monoxygenase (AHH: aryl hydrocarbon hydroxylase) activity toward benzo(a)pyrene and NADPH-cytochrome C (P-450) reductase activity were assayed. Uninduced AHH activities were undetectable or very low; induction of AHH with benz(a)anthracene (BA) alone, and especially with BA aminophylline, increased activity substantially without changing the fluorescence spectra of the products. Preparations of RAG cells were apparently able to support oxygenation of benzo(a)pyrene by cytochrome P-448 to the same extent as with purified cytochrome c reductase. Presence of AHH activity in hybrid lines suggests that the structural gene of PAH-inducible monoxygenase or the gene(s) involved in enzyme induction are on human chromosome 2. However, a role for the mouse genes in expression of induced AHH cannot be ruled out. (32 Refs)

79. BIOCHEMICAL LOCALIZATION OF ARYL HYDROCARBON HYDROXYLASE IN THE INTESTINAL EPITHELIUM OF THE RAT.

Porter CW, Dworaczyk D, Gurtoo HL
Dept. Experimental Therapeutics, Grace Cancer Drug Center, Roswell Park Memorial Inst., New York State Dept. Health, Buffalo, NY, 14263
Cancer Res; 42(4):1283-1285 1982

The distribution of the carcinogen-metabolizing enzyme system, aryl hydrocarbon hydroxylase (AHH), was biochemically determined in the intestinal epithelium of the rat. A method of epithelial cell isolation in which fractions of cells are sequentially collected as a villus tip-to-crypt gradient was used. AHH activity was highest in the midvillus region, 40% lower at the villus tip, and practically nonexistent in the crypt region where active cell proliferation takes place. This distribution differed from those of sucrase and alkaline phosphatase (used here as markers for cellular differentiation), which were characteristically lowest in activity at the crypts and increased continuously to the villus tips. Conceivably, the midvillus peak of AHH activity may serve to protect or enhance the susceptibility of cells undergoing cell division in the nearby crypt regions, depending on whether the predominant function of AHH in the intestinal epithelium involves detoxication or activation of polyaromatic carcinogens. (Author abstract) (16 Refs)

ALTERATION OF OTHER CARCINOGEN-METABOLIZING ENZYMES BY CARCINOGENS

80. PLASMA ALPHA-FETOPROTEIN ELEVATION AND MUTAGENICITY OF URINE AS EARLY PREDICTORS OF CARCINOGENICITY IN BENZO(A)PYRENE FED RATS.

Boyd JN, Misslbeck N, Babish JG, Campbell TC, Stoewsand GS
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Drug Chem Toxicol; 4(3):197-205 1981

Weanling male Fischer rats were fed on diets containing benzo(a)pyrene (BaP) at (a) 0 or 1,000 ppm or (b) 0, 1, or 100 ppm for 11 wk on diet (a) or 8 wk on diet (b). Some of the animals' diet contained 500 ppm sodium phenobarbital (PB) for the last 5 wk (none getting 1,000 ppm BaP). Cardiac blood was obtained weekly at wk three and assayed for alpha-fetoprotein (AFP). Hepatic slices were obtained at wk six and stained for gamma-glutamyl transpeptidase (GGT) activity. Also at wk six 8-hr urine samples were taken and assayed by the Salmonella/mammalian microsomal test with S typhimurium strain T98. The AFP level was independent of all diets except for notable elevation at wk six in the 1,000 ppm BaP animals. Except for 1,000 ppm BaP animals assay for GGT was independent of other variables. The mutagenesis assay was positive only for the 1,000 ppm BaP animals at wk six with and without activation, and for the 100 ppm BaP with PB animals at wk eight with activation. The AFP and urinary mutagenesis assays were recommended as co-tests for short term carcinogenicity potential evaluation. (12 Refs)

81. CYTOCHEMICAL MARKERS OF BLADDER CARCINOGENESIS.

Wilson PD, Summerhayes IC, Hodges GM, Trejdosiewicz LK, Nathrath WJ
Physiologisches Institut der Universitat Munchen, Pettenkoferstrasse 12, 8 Munchen 2, W. Germany
Histochem J; 13(6):989-1007 1981

Enzyme cytochemical and immunocytochemical techniques were used at the light and electron microscope levels to study the distribution of potential enzyme and antigen markers of chemical transformation in rat and mouse bladders. In in vivo methylnitrosourea-induced rat tumors, alkaline phosphatase (AP) localization was normal on the external surface of the plasma membranes of some cells whereas in others AP was detected only on intracellular membranes. 5'-Nucleotidase (5NU) localization was abnormal in all cells, being seen on endoplasmic reticulum and nuclear membranes only, while in normal bladders only ectoenzyme localization was seen. After tumors were cultured as explants for 15 days, heterogeneity of AP and 5NU localization was seen on the plasma membranes. Enzyme production within some cells was variable while in other cells, only parts of the membrane reacted heavily. A bimodal pattern of AP localization was seen in transformed cell cultures and tumors of mouse bladder derived by in vitro treatment of explants with dimethylbenz(a)anthracene. Cells had either normal ectoenzyme reaction product or abnormal intracellular membrane reaction product. 5NU and adenosine diphosphatase were lost and an Mg.ATPase and a cyclic AMP-independent, calcium-insensitive 'protein phosphatase' were induced in transformed cell cultures. Immunocytochemical study revealed an epithelial antigen in the cytoplasm of both normal and transformed cells which was associated with reticular cytoplasmic ground substance, plasma membrane vesicles and cytoskeletal elements. (29 Refs)

82. FACTORS THAT AFFECT INTESTINAL BACTERIAL ACTIVITY: IMPLICATIONS FOR COLON CARCINOGENESIS.

Goldin BR, Lombardi P, Mayhew J, Gorbach SL, Tannenbaum SR, Wilkins TD, Reddy BS, Goldman P, Hill DH, Montesano R, Magee PN, Strobel HW
Dept. Medicine, Infectious Disease Services, Tufts-New England Medical Center, Boston, MA, 02111
Banbury Rep; 7:41-57 1981

Several experiments in male Fischer rats showed significant dietary effect on fecal beta-glucuronidase (B-Gase), nitroreductase (NRase), and azoreductase (AzRase) activities. Diets containing high levels of beef protein or beef fat were associated with a significant increase in these enzymes. The metabolic conversion of 2-nitronaphthalene (2-NN) or 2-naphthylamine-beta-D-glucuronide to 2-naphthylamine (an index of NRase activity) was significantly higher in beef-fed rats than in grain-fed controls. Dietary supplementation with Lactobacillus acidophilus, tetracycline, or erythromycin reduced fecal enzyme activities in the meat fed rats to those in controls. The mutagenicity of 2-NN in a NRase-negative Salmonella strain was enhanced in the presence of liver microsomes only by a fecal extract containing NRase activity. Significant dietary effects on fecal enzyme activity were also observed in American adults (20-35 yr old). Lacto-vegetarians and strict vegetarians showed lower fecal B-Gase, NRase, AzRase, and 7-alpha-dehydroxylase activities than omnivores. No major differences were noted between the two vegetarian groups. Dietary supplementation with Lactobacillus caused decreases in fecal B-Gase, NRase, and AzRase activities in omnivores. The enzyme activities returned to baseline values after the supplementation was stopped. The high-animal protein and high-animal fat diets, which are associated with an increased risk of colorectal cancer, caused an increase in bacterial enzymes capable of generating carcinogens in the colon in the rats. The similar association between dietary habits and fecal enzyme activities in humans may provide a partial explanation for the strong positive correlation between daily beef and fat consumption and the incidence of colorectal cancer. (11 Refs)

83. ENZYMES OF NORMAL, PREMALIGNANT, AND MALIGNANT COLONIC CELLS.

Balis ME, Higgins PJ, Salser JS, Stemmerman GN, Magee PN, Wattenberg LW
Dept. Cell Metabolism and Cell Biochemistry, Memorial Sloan-Kettering Cancer Center, New York, NY, 10021
Banbury Rep; 7:129-139 1981

The villus and crypt cells of rat small intestine contained two different forms of adenosine deaminase (AD) and adenine phosphoribosyltransferase (APRT). The APRTs of normal and neoplastic rat colonic mucosa showed similar properties. Normal colonic mucosa showed predominantly one form of

AD, but colonic tumors induced by methylazoxymethanol showed two distinct forms. The ADs of human colonic mucosa and colonic cancer were also distinctive. The tumor AD was smaller than that of normal tissue and was also immunologically distinct. In rat colon, ornithine decarboxylase (ODC) activity was about the same as in liver and only 1-2% that of the small intestine. Carcinogens caused a marked increase in the ODC activity of the target tissue: acetylaminofluorene in the liver, and dimethylhydrazine (DMH) in the colon. Thymidine kinase (TK) activity of the intestine was much higher in the fetal rat than in young or mature rats. After the administration of a colonic carcinogen (DMH), the colonic TK activity increased to levels resembling the fetal TK activity. Assays using rabbit antisera demonstrated two types of TK in normal human intestine, representing the flat mucosa and the crypts. A rabbit antibody against TK from human term placenta cross-reacted against cells from a number of tumor types, including abnormal cervical cells in Papanicolaou smears and colon carcinoma cells. This antibody also reacted with skin fibroblasts from patients with familial colonic polyposis. The specificity of the TK antibody for a variety of tumor types was greatly reduced by preabsorbing the rabbit antiserum with normal human colon extracts. (11 Refs)

84. EFFECT OF STYRENE ON HEPATIC MIXED FUNCTION OXIDASES, GLUTATHIONE CONTENT AND GLUTATHIONE-S-TRANSFERASE ACTIVITY IN RATS.

Das M, Dixit R, Mushtaq M, Srivastava SP, Seth PK
Industrial Toxicology Res. Centre, Mahatma Gandhi Marg, P.O. Box 80, Lucknow-226001, India
Drug Chem Toxicol; 4(3):219-227 1981

Adult male albino rats given 7 consecutive daily doses of styrene at 270, 450, or 900 mg/kg were assayed for changes in their hepatic enzymes on the 8th day. Glutathione was suppressed at the highest dose, while glutathione-S-transferase was suppressed at the middle and highest doses. Both higher doses elevated arylhydrocarbon hydroxylase, aniline hydroxylase, aminopyrine-N-demethylase, and ethylmorphine-N-demethylase. These results implicate styrene as a potential enhancer of polycyclic aromatic hydrocarbon carcinogenicity. (14 Refs)

85. ISOLATION AND IDENTIFICATION OF KAHWEOL PALMITATE AND CAFESTOL PALMITATE AS ACTIVE CONSTITUENTS OF GREEN COFFEE BEANS THAT ENHANCE GLUTATHIONE S-TRANSFERASE ACTIVITY IN THE MOUSE.

Lam LK, Sparnins VL, Wattenberg LW
Dept. Lab. Medicine and Pathology, Univ. Minnesota, Minneapolis, MN, 55455
Cancer Res; 42(4):1193-1198 1982

Glutathione S-transferase is a major detoxification enzyme system that catalyzes the binding of a variety of electrophiles, including reactive forms of chemical carcinogens, to glutathione (GSH). Green coffee beans fed in the diet induce increased GSH S-transferase activity in the mucosa of the small intestine and in the liver of mice. A potent compound that induces increased GSH S-transferase activity was isolated from green coffee beans and identified as kahweol palmitate. The corresponding free alcohol, kahweol, and its synthetic monoacetate are also potent inducers of the activity of GSH S-transferase. A similar diterpene ester, cafestol palmitate, isolated from green coffee beans was active but less so than was kahweol palmitate. Likewise, the corresponding alcohol, cafestol, and its monoacetate showed moderate potency as inducers of increased GSH S-transferase activity. Kahweol palmitate and cafestol palmitate were extracted from green coffee beans into petroleum ether. The petroleum ether extract was fractionated by preparative normal-phase and reverse-phase liquid chromatographies successively. Final purification with silver nitrate-impregnated thin-layer chromatography yielded the pure palmitates of cafestol and kahweol. The structures were determined by examination of the spectroscopic data of the esters and their parent alcohols and by derivative comparison. (Author abstract) (22 Refs)

86. REGULATION OF GAMMA-GLUTAMYLTRANSPEPTIDASE IN RAT HEPATOCYTE MONOLAYER CULTURES.

Edwards AM
Clinical Biochemistry, Sch. Medicine, Flinders Univ. South Australia, Bedford Park, South Australia 5042, Australia
Cancer Res; 42(3):1107-1115 1982

Hepatocytes isolated as a relatively pure population from normal adult rats were maintained in primary monolayer culture for 4 to 7 days on plastic dishes. Factors affecting activity of gamma-glutamyltranspeptidase (GGT) in culture were investigated to establish a basis for in vitro studies on carcinogen-induced changes in GGT. Freshly plated cultures contained few GGT-positve cells (0.4%) and very low total GGT activity, but with all media tested, activity increased progressively with time in culture, the extent of increase depending on medium composition. For hepatocytes in modified Waymouth medium alone (control cultures), there was a slow rise in activity after a 1-to 2-day lag period. This increase was enhanced up to 10-fold in the presence of 3 uM dexamethasone for cells on plastic but only 2-to 3-fold for cells on collagen gels. The time- and dose-dependent action of dexamethasone was prevented by cycloheximide, partly blocked by actinomycin D, and reversed after several hr by removing the steroid, when GGT activity decreased with a max half-life of 60 to 80 hr. These observations suggest that dexamethasone caused reversible enzyme induction dependent on continuing RNA and protein synthesis. Cell maintenance with fetal calf serum or with N6,mO2'-dibutyryl adenosine 3':5'-monophosphate or glucagon markedly reduced the extent of induction by dexamethasone and slightly lowered activity in control cultures. Maintenance at lower pH within the range of 7.2 to 7.8 or at higher glucose concentrations within the range of 2.8 to 28 mM also resulted in markedly lower GGT activities in control or dexamethasone-induced cultures. Glucose repression was independent of insulin concentration. The reversible induction and repression of GGT may reflect broad changes in hepatocyte gene expression rather than specific controls of GGT function. Since GGT in cultured hepatocytes is subjected to regulation by a variety of noncarcinogens, caution is required in its use as a preneoplastic marker. Nevertheless, the identification of culture media which preserve low activity may allow studies on carcinogen-induced changes in GGT as a probe of the early events in vitro hepatocarcinogenesis. (Author abstract) (62 Refs)

87. HAEM AND DRUG-METABOLIZING ENZYMES IN REGENERATING RAT LIVER.

Srivastava RC, Dwivedi RS, Kaur G, Srivastava R
Industrial Toxicology Res. Center, P.O. Box No. 80, Mahatma Gandhi Marg, Lucknow-226001, India
Br J Exp Pathol; 63(1):1-4 1982

Various parameters of heme and drug metabolism were measured during the course of liver regeneration after two-thirds hepatectomy. Partial hepatectomy produced a significant depression in delta-ALA synthetase and delta-ALA dehydratase, and induction in heme oxygenase at an early stage of regeneration. The values returned to normal within 7-14 days. These changes were also accompanied by a marked decline in benzo(a)pyrene hydroxylase and aminopyrene demethylase. The level of glutathione and the activity of glutathione reductase also increased during the early stage of proliferation. The increased level of glutathione with concomitant decrease in drug-metabolizing enzymes and induction in heme oxygenase could be considered as a protective mechanism for the detoxication process, although a contribution from other biotransforming mechanisms cannot be excluded. (Author abstract) (23 Refs)

REVIEWS AND OTHER RELEVANT STUDIES

88. METABOLIC INTERACTIONS OF HYDROCARBONS WITH MAMMALIAN LUNG.

Smith BR, Bend JR
Lab. Pharmacology, Natl. Inst. Environmental Health Sciences, NIH, Research Triangle Park, NC, 27709
Rev Biochem Toxicol; 3:77-122 1981

Lung interactions with aliphatic, alkylated aromatic, and polycyclic aromatic hydrocarbons are reviewed. Emphasis is placed on the metabolic mechanisms responsible for detrimental effects to the lungs following exposure to these compounds. Included in the discussion of aromatic hydrocarbons and the lungs are considerations of the effects of exposure to smoke and inducing agents, benzopyrene metabolism in perfused lungs, hydrocarbon metabolism as a test for identification of individuals predisposed to develop lung cancer, and hydrocarbon metabolism in human lungs. (163 Refs)

89. QUANTITATIVE CORRELATIONS AMONGST ALKALINE DNA FRAGMENTATION, DNA COVALENT BINDING, MUTAGENICITY IN THE AMES TEST AND CARCINOGENICITY, FOR 21 COMPOUNDS.

Parodi S, Taningher M, Boero P, Santi L
Istituto Scientifico per lo Studio e la Cura dei Tumori, Viale Benedetto XV, 10 I-16132 Genova, Italy
Mutat Res; 93(1):1-24 1982

Correlations between the carcinogenicity of 21 compounds and the alkaline DNA fragmentation, formation of DNA adducts, and Ames-test mutagenicity produced by the compounds were studied. Test compounds included 6 methylating agents, 3 ethylating agents, 5 aromatic amines, 2 polycyclic aromatic hydrocarbons, and 5 heterogeneous compounds thought to generate DNA adducts with greater steric hindrance than those produced by methylating or ethylating agents. Compounds were administered to adult mice and rats by oral and parenteral routes. The highest doses exceeded lethal levels. Parameters measured included the oncogenic potency index (OPI), covalent binding index (CBI), DNA fragmentation index (DFI), mutagenic potency index (MPI), and lethal dose index (LDI). All parameters were found to be correlated with carcinogenic potency; the correlation between CBI in vivo and carcinogenicity was 3x as great as the correlation between the MPI and carcinogenicity. CBI in vivo correlated strongly with DFI in vivo. Assay of the DFI for eight compounds indicated negative results for benzo[a]pyrene, 7,12-dimethylbenz[a]anthracene, 2-acetylaminofluorene, and urethane; positive results were obtained for methyl methanesulfonate, aniline, 2-naphthylamine, and benzidine. Results indicate that carcinogenic potential should be predictable from the results of a battery of appropriate tests. (28 Refs)

90. THE USE OF MAMMALIAN CELL MUTANTS TO STUDY THE MECHANISMS OF CARCINOGENESIS.

Trosko JE, Chang CC, Warren ST, Liu PK, Wade MH, Tsushimoto G
Dept. Pediatrics and Human Development, Michigan State Univ., Coll. Human Medicine, East Lansing, MI, 48824
Gann Monogr Cancer Res; 27:159-179 1982

Use of mammalian cell mutants to study the mechanisms of carcinogenesis is reviewed. A genetic approach was used to study molecular mechanisms of initiation and promotion. It was shown that different mutagens induce different types of mutations and that phenotypic expression is influenced by tumor promoters or antipromoters, while mutation fixation is not. General considerations of in vitro mutagenesis at the gene level are discussed. Study of mutagen-sensitive DNA-repair deficient mutants and xeroderma pigmentosum and Bloom's syndrome cells demonstrated that a defect in DNA repair or DNA replication may cause mutagenesis. An in vitro assay to detect tumor promoters was designed with the basic premise that all tumor promoters block metabolic cooperation. Inhibition of cell-cell communication by known tumor promoters might be one of the initial events triggered by tumor promoters. It is possible to study the mechanism of tumor promoters and to screen for environmental promoters. An hypothesis for the relationship of metabolic cooperation and carcinogenesis is proposed. (144 Refs)

91. DISCUSSION: COLONIC ACTIVATION OF CARCINOGENS.

Wogan GN, Montesano R, Goldin BR, Reddy BS, Magee PN, Archer MC, Goldman P, Balish E, Newmark H, Venitt S, Wattenberg LW, Strobel HW
Massachusetts Inst. Technology, Boston, MA
Banbury Rep; 7:167-172 1981

Experiments in rat colon explants exposed to benzo(a)pyrene (BP) suggest that the colon can fully activate this series of carcinogens by the same pathways as those observed in other tissues. A tissue's sensitivity to a carcinogen is related to its capacity to activate the carcinogen (although the site of metabolic activation is not necessarily the site of tumorigenesis) and its capacity to repair DNA dam age induced by that chemical. To a certain extent, the known inhibitors of carcinogenesis can be divided into two groups. Some inhibitors cause 'phase 2' detoxification (essentially, conjugation) reactions; they alter the metabolism of the mixed function oxidase (MFO) system but do not increase its activity. In the case of BP, the effect of a 'phase 2'-active inhibitor is to reduce the formation of the ultimate carcinogen. The other inhibitors of carcinogenesis, for which beta-naphthoflavone is a prototype, caused both 'phase 1' and 'phase 2' reactions. MFO activity is enhanced. These agents simultaneously induce oxidative reactions (often leading to activation of the carcinogen) and enhanced detoxification reactions. The net result in most cases is protection of the host against the carcinogen. (8 Refs)

92. IMPLICATIONS OF DIETARY FIBER BREAKDOWN IN THE HUMAN COLON.

Cummings JH, Stephen AM, Branch WJ
MRC Dunn Clinical Nutrition Centre, Old Addenbrookes Hosp., Cambridge, CB2 IQE, England
Banbury Rep; 7:71-81 1981

Metabolism of fiber in the colon and implications for human carcinogenesis are reviewed. Possible hypotheses for the mechanism of the protective effect can be obtained from examining data on the dominant effects of fiber on colorectal function. Dietary fiber is extensively degraded in the colon, leading to production of short-chain fatty acids (butyrate) which may affect colonic cell function. Fiber breakdown also stimulates microbial growth in the colon, leading to increased bulk of the colonic content, faster transit rate, and rerouting of nitrogen metabolism. Fiber fermentation in the colon diverts nitrogen metabolism from ammonia formation (ammonia is more toxic to normal cells than transformed cells) to bacterial protein synthesis. If endogenous nitrite synthesis occurs in the human colon, it may arise from the oxidation of ammonia. The optimum pH for bacterial nitrification in pure cultures and natural ecosystems is alkaline (7.0-8.5). A metabolic consequence of a high-fiber diet may be reducing the colonic pH to a level unfavorable to nitrite synthesis from ammonia, leading to a reduced formation of N-nitroso compounds. The urinary excretion of protein metabolites other than ammonia declines when wheat fiber is added to the diet, showing another change in the direction of nitrogen metabolism in the colon. Any or all these events may be important in protection from colorectal cancer. (56 Refs)

93. BIOLOGICAL OXIDATION OF NITROGEN IN ORGANIC COMPOUNDS AND DISPOSITION OF N-OXIDIZED PRODUCTS.

Hlavica P
Inst. Pharmacology and Toxicology, Univ. Munich, Munich, W. Germany
CRC Crit Rev Biochem; 12(1):39-101 1982

The most important findings concerning biotransformation of nitrogen-containing molecules to N-oxidized products, including mutagens and carcinogens, are reviewed. Chemical aspects, in cluding classification and chromatographic methods, and occurrence of N-oxidation products in microorganisms, plants, and animals are discussed. N-oxidation of amine compounds is reviewed, with a list of compounds shown to be excreted in the urine as N-oxidation products. Enzymology of N-oxidation in the endoplasmic reticulum is emphasized, with discussion of cytochrome P-450, mixed function amine oxidase, and peroxidase-dependent reactions. Reduction, further oxidation, N-dealkylation, deamination, rearrangement, acylation and deacylation, and miscellaneous reactions of N-oxidized compounds to yield secondary metabolites, some stable and some highly reactive with macromolecular cell constituents, are described. (440 Refs)

94. CORRELATION OF ALKYLATING AND MUTAGENIC ACTIVITIES OF ALLYL AND ALLYLIC COMPOUNDS: STANDARD ALKYLATION TEST VS. KINETIC INVESTIGATION.

Eder E, Neudecker T, Lutz D, Henschler D
Inst. Toxicology, Univ. Wurzburg, D-8700 Wurzburg, W. Germany
Chem Biol Interact; 38(3):303-315 1982

Thirty-nine allylic and non-allylic compounds have been tested in the standard 4-(p-nitrobenzyl)pyridine (NBP) alkylating procedure and the Salmonella typhimurium mutagenicity assay. Fourteen of these were found directly mutagenic (without addition of S-9 mix activating enzyme system). With 12 of these compounds, a good correlation of alkylating and mutagenic potencies was established; the remaining 2 do not meet the chemical conditions of the NBP procedure on account of HCL elimination with these 2 compounds. The other 25 substances were inactive in both systems. The quantitative correlation proved to be almost linear in the lower activity ranges (E approx 2; revertants/umol approx 600). The reasons for some deviations from the linear relationship have been analyzed and discussed on the basis of structural features. In addition to the standard alkylation test, a modified NBP-test was performed in order to obtain kinetic data and activation energy values. The results with six representative allylic compounds show that the overall correlation is not substantially improved above that of the standard procedure; nonetheless, additional information on reaction characteristics is obtained with some substances. (Author abstract) (26 Refs)

95. THE TOXICOLOGY OF COCOA AND METHYLXANTHINES: A REVIEW OF THE LITERATURE.

Tarka SM
Life Sciences, Hershey Foods Corp., Corporate Technical Center, Hershey, PA
CRC Crit Rev Toxicol; 9(4):275-312 1982

Toxicology of cocoa and methylxanthines (caffeine, theobromine, and theophylline) was discussed with respect to the following: physical properties; toxic effects of cocoa and theobromine in the diets of various animals; biological effectiveness of the methylxanthines in cocoa; toxicity of methylxanthines: distribution, metabolism, and excretion in animals and humans (metabolism during pregnancy, la ctation, and growth; diet and drug influence on methylxanthine metabolism); pharmacological properties of the methylxanthines; effects of methylxanthines on growth and other physiological processes; effects on reproduction; teratogenesis; mutagenesis; chronic toxicity/carcinogenesis; SCOGS report; and fibrocystic breast disease. Research on teratogenic and mutagenic effects of caffeine was thought to be relatively abundant, but there are only a few reports on the carcinogenic effects of caffeine and none on such effects of cocoa powder, theobromine, theophylline, or tea. (203 Refs)

96. REVIEWS IN BIOCHEMICAL TOXICOLOGY.

Hodgson E, Bend JR, Philpot RM
North Carolina State Univ., Raleigh, NC
Rev Biochem Toxicol 3: 368 pp., 1981.

Topics discussed in relation to biochemical toxicology include the following: xenobiotic-metabolizing enzymes (identification and purification of multiple forms of uridine diphosphate-glucuronosyltransferase; organic sulfur substrates for the microsomal flavin-containing monooxygenase), biochemical toxicology of organs and organ systems (properties of distribution of enzymes of pulmonary cytochrome P-450-dependent monooxygenase systems; metabolic interactions of hydrocarbons with mammalian lung), toxic compounds (biochemical toxicology of benzene; metabolic activation and detoxification of aflatoxins), modes of toxic action (mechanisms of fibrosis and cellular and biochemical mechanisms of mouse skin tumor promoters), methodology of biochemical toxicology (use of model systems in biochemical toxicology heme models), comparative toxicology (metabolism of aromatic hydrocarbons by bacteria, fungi, and algae). (1276 Refs)

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This document contains summaries of over 1200 open experimental clinical cancer therapy protocols from countries around the world.

Open protocols are arranged in sections according to the specific ty of cancer.

Protocols closed in 1981 are listed by title, number, and investigato in a separate section.

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- Tumor index
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NOTICE OF CURRENT REVIEWS: CARCINOGENESIS

As an additional service to readers of carcinogenesis (CK series) CANCERGRAMS, each issue now provides a bibliography of review articles of interest to carcinogenesis researchers, selected from journals screened for that month's CANCERGRAMS.

CHEMICAL CARCINOGENESIS

1. IARC MONOGRAPHS ON THE EVALUATION OF THE CARCINOGENIC RISK OF CHEMICALS TO MAN. SOME ANTINEOPLASTIC AND IMMUNOSUPPRESSIVE AGENTS.
Schmahl D
International Agency for Cancer Research, Lyon, France
IARC Mongr Eval Carcinog Risk Chem Hum 26: 411 pp., 1981.

2. BIOCHEMICAL TOXICOLOGY OF BENZENE.
Snyder R, Longacre SL, Witmer CM, Kocsis JJ, Andrews LS, Lee EW
Dept. Pharmacology, Thomas Jefferson Univ., Philadelphia, PA, 19107
Rev Biochem Toxicol; 3:123-153 1981

3. A REVIEW OF THE MUTAGENICITY OF CHROMIUM
Hatherill JR
Toxicology, Sch. Public Health, Univ. Michigan, Ann Arbor, MI, 48109
Drug Chem Toxicol; 4(3):185-195 1981

4. HORMONES AND BREAST CANCER.
Pike MC, Siiteri PK, Welsch CW
Dept. Family and Preventive Medicine, Univ. Southern California Sch. Medicine, Los Angeles, CA, 90033
Banbury Rep 8: 491 pp., 1981.

5. ORAL CONTRACEPTIVES: VOLUME 5.
Briggs MH, Briggs M
Deakin Univ., Geelong 3217, Australia
Oral Contraceptives: Volume 5. St. Albans, VT, Eden Medical Research Inc., Annual Research Reviews--Endocrinology, 321 pp., 1981.

6. EPIDEMIOLOGICAL STUDIES OF THE ROLE OF EXOGENOUS ESTROGENS IN THE ETIOLOGY OF BREAST CANCER.
Kelsey JL, Bulbrook RD, Korenman SG, Siiteri PK, Henderson BE
Dept. Epidemiology and Public Health, Yale Univ. Sch. Medicine, New Haven, CT, 06510
Banbury Rep; 8:215-228 1981

7. EFFECTS OF LONG-TERM EXPOSURE TO LOW LEVELS OF OZONE: A REVIEW.
Melton CE
Civil Aeromedical Inst., Federal Aviation Admin., Oklahoma City, OK, 73125
Aviat Space Environ Med; 53(2):105-111 1982

8. METABOLIC INTERACTIONS OF HYDROCARBONS WITH MAMMALIAN LUNG.
Smith BR, Bend JR
Lab. Pharmacology, Natl. Inst. Environmental Health Sciences, NIH, Research Triangle Park, NC, 27709
Rev Biochem Toxicol; 3:77-122 1981

9. REVIEW OF EXPERIMENTAL CARCINOGENESIS BY COMPOUNDS RELATED TO VINYL CHLORIDE
Chu KC, Milman HA
NCI, Bethesda, MD, 20205
Environ Health Perspect; 41:211-220 1981

10. REVIEWS IN BIOCHEMICAL TOXICOLOGY.
Hodgson E, Bend JR, Philpot RM
North Carolina State Univ., Raleigh, NC
Rev Biochem Toxicol 3: 368 pp., 1981.

DIETARY FACTORS IN CARCINOGENESIS

11. ALCOHOL AND CANCER.
MacSween RN
Univ. Dept. Pathology, Western Infirmary, Glasgow, Scotland
Br Med Bull; 38(1):31-33 1982

12. THE TOXICOLOGY OF COCOA AND METHYLXANTHINES: A REVIEW OF THE LITERATURE.
Tarka SM
Life Sciences, Hershey Foods Corp., Corporate Technical Center, Hershey, PA
CRC Crit Rev Toxicol; 9(4):275-312 1982

13. IMPLICATIONS OF DIETARY FIBER BREAKDOWN IN THE HUMAN COLON.
Cummings JH, Stephen AM, Branch WJ
MRC Dunn Clinical Nutrition Centre, Old Addenbrookes Hosp., Cambridge, CB2 IQE, England
Banbury Rep; 7:71-81 1981

14. BILE SALTS AND OTHER CONSTITUENTS OF THE COLON AS TUMOR PROMOTERS.
Reddy BS, Tannenbaum SR, Montesano R, Correa P, Haenszel W, Wattenberg LW
Div. Nutrition, American Health Foundation, Naylor Dana Inst. for Disease Prevention, Valhalla, NY, 10595
Banbury Rep; 7:345-363 1981

15. MOLD PRODUCING CARCINOGENIC TOXINS IN FOOD PRODUCTS.
Preda N
Institutul de medicina si farmacie, Cluj-Napoca, Romania
Rev Chir [Oncol]; 20(1):1-9 1981
In RUM

16. THE MEANING OF CANCER 'DIETS'.
Jungi WF
Abt. f. Onkologie-Hamatologie, Medizinische Klinik C, CH-9007 St. Gallen, Switzerland
MMW; 124(2):26-28 1982
In GER

EPIDEMIOLOGY, ETIOLOGY AND GENETIC ASPECTS OF HUMAN CANCER

17. RISK FACTORS FOR CERVICAL CANCER.
Hulka BS
Dept. Epidemiology, Rosenau Hall 201H, Univ. North Carolina, Chapel Hill, North Carolina, NC, 27514
J Chronic Dis; 35(1):3-11 1982

18. EPIDEMIOLOGY OF THE MOST FREQUENTLY OCCURRING TUMORS OF THE DIGESTIVE SYSTEM.
Naujoks-Heinrich S, Dolle W
Abteilung Innere Medizin I, Universitatsklinik, Otfried-Muller-Strasse 10, D-7400 Tubingen, W. Germany
Internist (Berlin); 23(1):1-9 1982
In GER

19. BLADDER CANCER.
Skrabanek P, Walsh A
Endocrine Oncology Unit, Mater Misericordiae Hosp., Dublin, Ireland
UICC Tech Rep Ser 60: 192 pp., 1981.

20. RECENT ADVANCES IN CANCER CYTOGENETICS.
Pogosiants EE
All-Union Cancer Res. Center, Moscow, USSR
Genetika; 17(12):2087-2099 1981
In RUS

21. CURRENT STATUS OF CYTOGENETIC STUDIES IN ANIMAL TUMORS WITH SPECIAL REFERENCE TO NONRANDOM CHROMOSOME CHANGES.
Sasaki M
Chromosome Res. Unit, Hokkaido Univ., Faculty Science, Sapporo 060, Japan
Cancer Genet Cytogenet; 5(2):153-172 1982

ENVIRONMENTAL AND OCCUPATIONAL FACTORS IN CARCINOGENESIS

22. ASBESTOS-RELATED DISEASES.
Casey KR, Rom WN, Moatamed F
Building 512, RMCOEH, Univ. Utah Medical Center, Salt Lake City, UT, 84112
Clin Chest Med; 2(2):179-202 1981

23. NONASBESTOS FIBROUS MINERALS.
Lockey JE
Building 512, RMCOEH, Univ. Utah Medical Center, Salt Lake City, UT, 84112
Clin Chest Med; 2(2):203-218 1981

24. REVIEW OF EPIDEMIOLOGIC STUDY RESULTS OF VINYL CHLORIDE-RELATED COMPOUNDS.
Apfeldorf R, Infante PF
Office Carcinogen Identification and Classification, Health Standards, Programs, Occupational Safety and Health Admin. U. S. Dept. Labor, Washington, DC, 20210
Environ Health Perspect; 41:221-226 1981

25. CONCEPTS IN CAUSALITY: CHEMICALLY INDUCED HUMAN URINARY BLADDER CANCER.
Lower GM
Center Human Systems, Inst. Environmental Studies, Univ. Wisconsin, WARF Building, 610 Walnut St., Madison, WI, 53706
Cancer; 49(5):1056-1066 1982

CELLULAR AND MOLECULAR MECHANISMS IN CARCINOGENESIS

26. MOLECULAR MECHANISM OF ADAPTATION OF CELLS TO LOW LEVELS OF CARCINOGENIC AGENTS.
Villani G
Laboratoire de Pharmacologie et de Toxicologie Fondamentales, CNRS, 205, route de Narbonne, 31078 Toulouse Cedex, France
Pathol Biol (Paris); 30(2):117-123 1982
In FRE

27. MIGHT CANCER BE A FAILED RESPONSE TO RENEGADE MITOCHONDRIA?
Hartung J
Dept. Anesthesiology, State Univ. New York, Downstate Medical Center, Brooklyn, NY, 11203
J Theor Biol; 94(1):173-178 1982

MODIFICATION OF CARCINOGENESIS

28. EFFECT OF GEROPROTECTORS ON CARCINOGENESIS.
Anisimov VN
N. N. Petrov Res. Inst. Oncology, Leningrad, USSR
Usp Sovrem Biol; 92(3):455-472 1981
In RUS

29. RELATION OF NEUROLEPTIC DRUGS TO DEVELOPMENT AND GROWTH OF MAMMARY TUMORS.
Meites J, Aylsworth CF
Dept. Physiology, Neuroendocrine Res. Lab., Michigan State Univ., East Lansing, MI, 48824
Banbury Rep; 8:365-376 1981

30. THE ACTIONS OF INSULIN AS A HORMONAL FACTOR IN BREAST CANCER.
Hilf R, Siiteri PK, Shellabarger, Korenman SG, Rosen, Nandi
Dept. Biochemistry and Univ. Rochester Cancer Center, Univ. Rochester, Rochester, NY, 14642
Banbury Rep; 8:317-327 1981

VIRAL AND IMMUNOLOGICAL ASPECTS OF CARCINOGENESIS

31. ONCOGENES.
Bishop JM
Univ. California, San Francisco, CA
Sci Am; 246(3):80-84,87-92,154 1982

32. HUMAN CANCERS AND HUMAN VIRUSES.
Waterson AP
Royal Postgraduate Medical Sch., London W12 0HS, England
Br Med J; 284(6314):446-448 1982

33. THE IMMUNOLOGY OF CANCER OF THE HEAD AND NECK WITH PARTICULAR REFERENCE TO ORAL CANCER.
Scully C
Univ. Dept. Oral Medicine and Pathology, Immunology Unit, Glasgow Dental Hosp., 378 Sauchiehall St., Glasgow G2 3JZ, Scotland
Oral Surg; 53(2):157-169 1982

METHODOLOGY IN CARCINOGENESIS RESEARCH

34. THE USE OF MAMMALIAN CELL MUTANTS TO STUDY THE MECHANISMS OF CARCINOGENESIS
Trosko JE, Chang CC, Warren ST, Liu PK, Wade MH, Tsushimoto G
Dept. Pediatrics and Human Development, Michigan State Univ., Coll. Human Medicine, East Lansing, MI, 48824
Gann Monogr Cancer Res; 27:159-179 1982

35. BIOLOGICAL MONITORING IN THE IDENTIFICATION OF THE CANCER RISK OF INDIVIDUALS EXPOSED TO CHEMICAL CARCINOGENS.
Vainio H, Sorsa M, Rantanen J, Hemminki K, Aitio A
Inst. Occupational Health, Haartmaninkatu 1, SF-00290 Helsinki 29, Finland
Scand J Work Environ Health; 7(4):241-251 1981

36. A CRITICAL REVIEW OF BIOLOGICAL METHODS FOR THE DETECTION OF FUNGAL TOXINS IN FOODS AND FOODSTUFFS.
Watson DH, Lindsay DG
Food Science Div., Ministry of Agriculture, Fisheries, and Food, Great Westminster House, Horseferry Road, London SW1P 2AE, England
J Sci Food Agric; 33(1):59-67 1982

37. PITUITARY AND STEROID HORMONES IN RADIATION-INDUCED MAMMARY TUMORS.
Shellabarger CJ
Medical Dept., Brookhaven National Lab., Upton, NY, 11973
Banbury Rep; 8:339-351 1981

38. ASPERGILLUS NIDULANS: SYSTEMS AND RESULTS OF TESTS FOR CHEMICAL INDUCTION OF MITOTIC SEGREGATION AND MUTATION. I. DIPLOID AND DUPLICATION ASSAY SYSTEMS. A REPORT OF THE U. S. EPA GENE-TOX PROGRAM.
Kafer E, Scott BR, Dorn GL, Stafford R
Dept. Biology, McGill Univ., 1205 Ave. Docteur Penfield, Montreal H3A 1B1, Canada
Mutat Res; 98(1):1-48 1982

OTHER REVIEWS IN CARCINOGENESIS

39. MATHEMATICAL MODELS OF THE CELL CYCLE WITH A VIEW TO TUMOR STUDIES.
Bertuzzi A, Gandolfi A, Giovenco MA
Centro di Studio dei Sistemi di Controllo e Calcolo Automatici del C.N.R., Via Eudossiana 18, 00184 Rome, Italy
Math Biosci; 53(3/4):159-188 1981

40. NEOPLASMS IN DOMESTIC ANIMALS: A REVIEW OF EXPERIMENTAL AND SPONTANEOUS CARCINOGENESIS.
Madewell BR

Section Clinical Oncology, Dept. Veterinary Surgery, Univ. California, Davis, CA, 95616

Yale J Biol Med; 54(2):111-125 1981

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CHARLES HEIDELBERGER University of Southern California	*Mutagenesis and Oncogenic Transformation of Mouse Embryo Cells*	#VK04 54 min.
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MECHANISMS OF CARCINOGENESIS

Activation and Metabolism of Carcinogens

SERIES CK08 No. 82/08

AUGUST, 1982

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
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HE 20.3173/2:

METABOLIC ACTIVATION OF CARCINOGENS

1. METABOLISM OF BENZO(A)PYRENE IN RAT BY ORAL ADMINISTRATION.

Yamazaki H, Kumahashi H, Masuda N, Kishi T, Kakiuchi Y, Watabe K, Kondo M
(c/o Kakiuchi) Faculty Pharmaceutical Sciences, Kobe Gakuin Univ., 518, Arise, Igawadani, Tarumi, Kobe, 673, Japan
Chemosphere; 11(3):337-347 1982

Adult male Sprague-Dawley rats were given a single oral dose of tritiated (50 uCi) benzo(a)pyrene (BaP). They were sacrificed at hr 3, 7, 24, and 48. Organs, blood, and urine were assayed for BaP and metabolites. the urinary radioactivity was maximum at hr 7, decreasing slowly thereafter. Blood, kidney, liver, and lung radioactivity levels were all highest at hr 3, dropping sharply by hr 24. At hr 3 the liver contained a relatively high level of benzo(a)pyrene-9,10-diol, with lesser amounts of 3-hydroxybenzo(a)pyrene, benzo(a)pyrene-4,5-diol, benzo(a)pyrene-7,8-diol, benzo(a)pyrene-3,6-quinone, benzo(a)pyrene-1,6-quinone, and BaP. At hr 3 the kidney was highest in both quinones, with large amounts of all diols too. Peak amounts occurred in the lung at hr 7, mainly the two quinones and BaP; compared to all other sources the lung contained more metabolites and BaP at hr 48. At hr 3 in the blood the 9,10-diol and BaP were predominant; at hr 7, the 3-hydroxy metabolite prevailed. In contrast to the above sources, the urinary metabolites existed mainly as the glucuronides, mostly as the 3,6-quinone and 9,10-diol at hr 7. (19 Refs)

2. INDUCTION OF CYTOTOXICITY, MUTATION, CYTOGENETIC CHANGES, AND NEOPLASTIC TRANSFORMATION BY BENZO(A)PYRENE AND DERIVATIVES IN C3H/10T1/2 CLONE 8 MOUSE FIBROBLASTS.

Gehly EB, Landolph JR, Heidelberger C, Nagasawa H, Little JB
(c/o Heidelberger) Cancer Res. Lab., Univ. Southern Carlifornia Comprehensive Cancer Center, Los Angeles, CA, 90033
Cancer Res; 42(5):1866-1875 1982

Benzo(a)pyrene (BaP), a series of its metabolic derivatives, and benzo(e)pyrene, a very weakly carcinogenic isomer, were tested for their biological effects on transformable C3H/10T1/2 cells. These cells were used as targets in a series of assays designed to measure oncogenic transformation, mutation to ouabain resistance, cytotoxicity, and induction of cytogenetic changes, as evidenced by chromosomal aberrations and sister chromatid exchange. Of all the compounds tested, only the parent hydrocarbon, BaP, and (+-)-trans-7,8-dihydroxy-7.8-dihydrobenzo(a)pyrene were found to be significantly active in producing transformation and cytogenetic alterations. BaP, (+-)-trans-7,8-dihydroxy-7.8-dihydrobenzo(a)pyrene, and (+-)-7alpha,8beta-dihydroxy-9beta,10beta-epoxy-7,8,9,10 tetrahydrobenzo(a)pyrene however, were all effective inducers of mutation in C3H/10T1/2 cells. (+-)-7alpha,8beta-Dihydroxy-9beta,10beta-epoxy-7,8,9, 10-tetrahydrobenzo(a)pyrene was the most potent agent in tests for cytotoxicity Benzo(e)pyrene was inactive in all assays examined. Among the compounds tested, there was a correlation between the ability to induce cytogenetic changes and the ability to produce mutation and transformation. These results support the demonstrated role of (+-)-trans-7,8-dihydroxy-7,8-dihydrobenzo(a)pyrene as a proximal carcinogenic form of BaP and illustrate the utility of the C3H/10T1/2 cell system as an important tool for the detection of genotoxic damage by carcinogenic chemicals. (Author abstract) (47 Refs)

3. METABOLISM OF 3-HYDROXYBENZO(A)PYRENE IN RAT, ISOLATED HEPATOCYTES AND KIDNEY.

Yamazaki H, Kagita T, Fujiwara M, Kishi T, Kakiuchi Y, Watabe K, Kondo M
(c/o Xakiuchi) Faculty Pharmaceutical Sciences, Kobe Gakuin Univ., 518, Arise, Igawadani, Tarumi, Kobe, 673, Japan
Chemosphere; 11(3):349-353 1982

Adult male Sprague-Dawley rats were given an iv dose of tritiated (0.1 uCi) 3-hydroxybenzo(a)pyrene (3-OHBaP). Urine was collected at hr 24 and 48. The same amount of tritiated 3-OHBaP was also incubated with perfused rat hepatocytes and with sliced rat kidney at 37 C for 2 or 3 hr; extracts were obtained at hr 0.5, 1, 2, and 3 (kidney only). At hr 24 the urine contained benzo(a)pyrene-9,10-diol, benzo(a)pyrene-4,5-diol, benzo(a)pyrene-1,6-quinone, and 3-OHBaP. At hr 48 the urine still contained all of them, but the 9,10-diol was now present only as a glucuronide compared to none at hr 24. All of these metabolites and 3-OHBaP were found in the hepatocytes at all times except for no 1,6-quinone at hr 1, mainly as quinones at all times and 9,10-diol at hr 2. The 3-OHBaP was assayed only as a glucuronide; the 9,10-diol was never found as a glucuronide. In the kidney extracts only quinone metabolites were identifiable at hr 0.5 and 1. At hr 2 all the diols were present too, mainly 4,5-and 7,8-. At hr 3 not much change had occurred, but the 9,10-diol was present also as a glucuronide; 3-OHBaP was present as a glucuronide. (9 Refs)

4. IDENTIFICATION OF METABOLITES OF BENZO[B]FLUORANTHENE.

Amin S, LaVoie EJ, Hecht SS
Naylor Dana Inst. Disease Prevention, American Health Foundation, Valhalla, NY, 10595
Carcinogenesis; 3(2):171-174 1982

The metabolism by rat liver 9,000 x g supernatant of the environmental carcinogen benzo[b]fluoranthene was investigated. The major metabolites were identified by comparison to synthetic samples, as 5-and 6-hydroxybenzo[b]fluoranthene and 4- or 7-hydroxybenzo[b]fluoranthene. The principal dihydrodiol metabolite formed under these conditions was trans-11,12-dihydro-11,12 dihydroxybenzo[b]fluoranthene, which was identified by comparison to the synthetic compound. 1,2-Dihydro-1,2-dihydroxybenzo[b]fluoranthene was identified, by its mass spectrum and by comparison of its uv spectrum to that of a synthetic model compound, 11-ethylidene-11H-benzo[b]fluorene. No evidence was obtained for the formation of 7b,8-dihydro-7b,8-dihydroxybenzo[b]fluoranthene or trans-9,10-dihydro-9,10-dihydroxybenzo[b]fluoranthene. The latter would be the precursor to a bay region dihydrodiol epoxide of benzo[b]fluoranthene. (Author abstract) (24 Refs)

5. THE METABOLISM AND ACTIVATION OF POLYCYCLIC AROMATIC HYDROCARBONS IN EPITHELIAL CELL AGGREGATES AND FIBROBLASTS PREPARED FROM RAT MAMMARY TISSUE.

Cooper CS, Pal K, Hewer A, Grover PL, Sims P
Chester Beatty Res. Inst., Inst. Cancer Res., Royal Cancer Hosp., Fulham Road, London SW3 6JB, England
Carcinogenesis 3(2):203-210 1982

The metabolism of 7,12-dimethylbenz[a]anthracene (DMBA), benzo[a]pyrene (BP) and benz[a]anthracene (BA) by epithelial cell aggregates and fibroblasts in culture has been investigated using mammary tissue obtained from female Wistar rats. The results show that (a) both types of mammary cells metabolize all three hydrocarbons into ether- and water-soluble derivatives; (b) the patterns of metabolites produced by epithelial cells and fibroblasts are similar but that fibroblasts form more of the water-soluble materials; (c) the major dihydrodiols formed are the 8,9-dihydrodiols of BA and DMBA and the 7,8-and 9,10-dihydrodiols of BP; (d) all three hydrocarbons are metabolized to form products that bind covalently to protein but only the potent carcinogens BP and DMBA are metabolized to form derivatives that react covalently with DNA; and (e) the chromatographic profiles of the hydrocarbon-deoxyribonucleoside adducts formed in epithelial cells treated with either BP or DMBA are similar to those obtained in analogous experiments with fibroblasts. (Author abstract) (50 Refs)

6. FLUORO-SUBSTITUTED N-NITROSAMINES. 2. METABOLISM OF N-NITROSODIETHYLAMINE AND OF FLUORINATED ANALOGS IN LIVER MICROSOMAL FRACTIONS.

Janzowski C, Pool BL, Preussmann R, Eisenbrand G
Inst. Toxicology and Chemotherapy, German Cancer Res. Center, Im Neuenheimer Feld 280, D-6900 Heidelberg, W. Germany
Carcinogenesis; 3(2):155-159 1982

In vitro metabolism of N-nitrosodiethylamine (NDEA) and of its two fluorinated analogs N-nitroso-2,2,2-trifluoroethylethylamine (NDEA-F3) and N-nitroso-bis(2,2,2-trifluoroethyl)amine (NDEA-F6) was comparatively investigated using rat liver microsomes and S-9 fraction. Aldehydes, nitrite and unchanged nitrosamines were determined. Additionally the mutagenicity was measured in a Salmonella/mammalian microsome assay. NDEA and NDEA-F3 were deethylated and, to a smaller extent, denitrosated. Dealkylation of NDEA-F3 at the fluorinated ethyl group, however, was strongly inhibited. NDEA-F6 was practically not metabolized under the in vitro conditions used. In contrast to NDEA, the mutagenicity of NDEA-F3 was at best marginal; NDEA-F6 was not mutagenic. The results show that substitution of fluorine in beta-position of NDEA strongly influences alpha-C-hydroxylation and denitrosation. (Author abstract) (20 Refs)

7. METABOLIC ACTIVATION OF DIMETHYLNITROSAMINE TO MUTAGENS: ROLE OF CYTOCHROMES P-450 AND P-448.

Phillipson CE, Ioannides C, Parke DV
Biochemistry Dept., Univ. Surrey, Guildford, Surrey, GU2 5XH, England
Toxicol Lett; 11(1/2):95-101 1982

Activation of dimethylnitrosamine (DMN) by hamster liver mixed function oxidase enzymes after pretreatment with various inducing agents was investigated. Induction of liver microsomal enzymes in male hamsters was achieved by ip administration of phenobarbitone (PBT: 80 mg/kg body wt), 3-methylcholanthrene (MCA: 20 mg/kg), or Aroclor 1254 (A-1254: 500 mg/kg) for 3 days. Ethoxyresorufin O-deethylase (EOD), NADPH-cytochrome c reductase, and cytochrome P-450 activities were assayed in liver microsomal suspension by the Ames test. Cytochrome P-450 concentrations increased to 1.29, 1.53, and 2.16 nanomole/mg protein after induction with PBT, MCA, and A-1254, respectively, compared to control levels of 0.61 nanomole/mg protein. EOD levels increased to 1.99 and 0.72 nanomole/min/mg protein after induction with MCA and A-1254, respectively, compared to control levels of 0.32 nanomole/min/mg protein. EOD levels were unaffected by PBT. NADPH-cytochrome c reductase levels increased to 63 and 80 nanomole/min/mg protein after induction with PBT and A-1254, respectively, compared to control level of 44 nanomole/min/mg protein. Cytochrome c reductase was unaffected by MCA. Pretreatment with PBT, MCA, or A-1254 did not significantly alter the capacity of liver microsomes to activate DMN to mutagens. Dimethylnitrosamine dimethylase is either not involved in the metabolic activation of DMN, or is not the rate limiting step. (21 Refs)

8. RING- AND N-HYDROXYLATION OF 2-ACETYLAMINOFLUORENE BY RECONSTITUTED MOUSE LIVER MICROSOMAL CYTOCHROME P-450 ENZYME SYSTEM.

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Toxicol Lett; 11(1/2):173-179 1982

Ring and N-hydroxylation of 2-acetylaminofluorene with partially purified cytochrome P-450 and NADPH-cytochrome c reductase fractions from control and 3-methylcholanthrene (MC)-pretreated mice was investigated. MC pretreated mice produced a severalfold increase in both N- and ring hydroxylations. The specificity of N- and ring hydroxylation lies with the cytochrome P-450 fraction; the one obtained from MC-treated animals being more active than that from controls. (23 Refs)

9. AFLATOXIN M1: IN VITRO PREPARATION AND COMPARATIVE IN VITRO METABOLISM VERSUS AFLATOXIN B1 IN THE RAT AND MOUSE.

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Res Commun Chem Pathol Pharmacol; 35(3):467-490 1982

A rapid, simple and relatively inexpensive biotransformation method using microsomes from 3-methylcholanthrene (3MCA) pretreated rats is described for the production of aflatoxin M1 (AFM1) in sufficient quantities for metabolism studies. A comparison is made of the metabolism of AFM1 and AFB1 by the postmitochondrial (S-10) fraction from mouse and rat hepatocytes. AFM1, in both species, is metabolized more slowly than AFB1, with its major metabolites being found in the aqueous fraction and very little associated with S-10 protein. In contrast, AFB1 is metabolized to numerous chloroform-extractable, protein bound and water-soluble metabolites. The toxicological implications of reduced protein binding and slower metabolism for AFM1 are discussed. (Author abstract) (35 Refs)

10. TOXICITY AND METABOLISM OF ACRYLONITRILE.

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Med Pr; 32(1):25-33 1981

Studies in experimental animals and in vitro culture on the toxic effects and metabolism of acrylonitrile (AN) are reviewed. AN was found to be mutagenic for certain strains of Salmonella typhimurium and Escherichia coli. Increased incidence of tumors of the mammary glands, stomach, peripheral nervous system and sebaceous glands of the auditory meatus was found in female rats inhaling AN for 52 wk compared with controls. (40 Refs) (In POL)

11. METABOLISM OF BIS(2-CHLOROETHYL)ETHER AND BIS(2-CHLOROISOPROPYL)ETHER IN THE RAT.

Lingg RD, Kaylor WH, Pyle SM, Domino MM
U.S. Environmental Protection Agency, 26 W. St. Clair St., Cincinnati, OH, 45268
Arch Environ Contam Toxicol; 11(2):173-183 1982

Adult male CD-1 Sprague Dawley rats in individual cages were given a single po dose of bis(2-chloroethyl)ether (BCEE: 40 mg/kg) or bis(2-chloroisopropyl)ether (BCIE: 90 mg/kg). Both compounds contained a portion of 1-14C-labeled compound. Urine, feces, and expired air samples were taken for 48 hr, then the animals were sacrificed. Half of the radioactivity was eliminated in the urine and expired air in 12 hr for BCEE, and in 19 hr for BCIE, with relatively more of the BCIE in expired air. At 48 hr 81% of the BCEE radioactivity was recovered, 65% in urine, 11.5% in expired air, 2+% in feces, 2+% in organs and tissues, and less than 0.5% in cage wash; the corresponding figures (%) for BCIE were 73+, 47.5, 20−, 4, 2, and less than 0.5. Recovered percentages at 48 hr in blood, kidney, liver, and muscle were (BCEE and BCIE, respectively) 0.49 and 0.36, 0.56 and 0.10, 0.19 and 0.55, 0.96 and 0.50. No other localized concentrations exceeded 0.05%. Identified urinary metabolites (IUC) of BCEE consisted mostly of thiodiglycolic acid, with lesser amounts of 2-chloroethoxyacetic acid and N-acetyl-S-[2-(2-chloroethoxy)ethyl]-L-cysteine. IUC of BCIE were mainly 2-(2-chloro-1-methylethoxy)propanoic acid, half as much N-acetyl-S-(2-hydroxypropyl)-L-cysteine, and a second cysteine conjugate. Likely intermediate metabolites are discussed with regard to potential and known carcinogenicity and mutagenicity. (23 Refs)

OTHER METABOLISM OF CARCINOGENS

12. BENZO(A)PYRENE PHENOL PRODUCTION BY PERFUSED RAT LIVER AND ITS INHIBITION BY ETHANOL.

Reinke LA, McManus P, Kauffman FC, Thurman RG
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Cancer Res; 42(5):1681-1685 1982

A rapid and inexpensive method has been developed to estimate rates of benzo(a)pyrene phenol production by perfused rat liver. This method is based on the measurement of benzo(a)pyrene phenols utilizing a simple fluorometric procedure. Within 2 to 3 min after infusion of benzo(a)pyrene bound to serum albumin, phenols are excreted into the perfusate, primarily as glucuronide and sulfate conjugates. Maximal rates of phenol release were 8 to 10 nmol/g/hr in livers from control rats and 40 to 42 nmol/g/hr in livers from 3-methylcholanthrene-treated rats. Fasting of 3-methylcholanthrene-treated rats for 24 hr prior to perfusion experiments did not affect either the rate of phenol production or the extent of their conjugation. Ethanol (20 mM) inhibited rates of phenol formation by 50% in livers from fasted, 3-methylcholanthrene-treated rats but had no effect on benzo(a)pyrene hydroxylase activity in isolated hepatic microsomes. These data indicate that ethanol inhibits phenol formation from benzo(a)pyrene in intact liver, probably by diminishing the supply of the cofactor reduced nicotinamide adenine dinucleotide phosphate. (Author abstract) (22 Refs)

MODIFICATION OF CARCINOGEN METABOLISM

13. DIFFERENT PATTERNS OF BENZO[A]PYRENE METABOLISM OF PURIFIED CYTOCHROMES P-450 FROM METHYLCHOLANTHRENE, BETA-NAPHTHOFLAVONE AND PHENOBARBITAL TREATED RATS.

Gozukara EM, Guengerich FP, Miller H, Gelboin HV
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Carcinogenesis; 3(2):129-133 1982

An improved high-pressure liquid chromatography system was used to analyze the amount of benzo[a]pyrene metabolites formed in reconstituted microsomal mixed-function oxidase systems containing different cytochromes P-450. We separated 12 identified and 7 unknown metabolites of BP which included 3 diols: the 9,10-, 4,5-, and 7,8-dihydrodiols; 4 phenols, 9-, 7-, 1-, and 3-hydroxybenzo[a]pyrene (OH-BP); and 3 quinones: the 1,6-, 3,6-, and 6,12-quinones. Two additional peaks co-migrated with synthetic 4-OH-BP and 5-OH-BP, respectively. The former, designated fraction 1, was shown by uv spectra to contain primarily the 4,5-epoxide with small amounts of 4-OH-BP. The total metabolism of BP was found to be approx 20-fold greater with the cytochrome P-450 from the 3-methylcholanthrene (P-450 3-MC) and beta-naphthoflavone (P-450 BNF) treated rats than with the phenobarbital preinduced cytochrome P-450 (P-450 PB). 3-OH-BP and 9-OH-BP were the major phenolic products for both P-450 3-MC and P-450 BNF whereas the 3-OH-BP and 1-OH-BP were the major phenolic products for P-450 PB. The ratio of total phenols to diols was found to be 3.34, 4.85 and 0.70 for P-450 3-MC, P-450 BNF and P-450 PB. The major dihydrodiol generated by P-450 3-MC and P-450 BNF was 7,8-dihydroxy-7,8-dihydrobenzo[a]pyrene, whereas the 9,10-diol was the major diol from P-450 PB. The amount of 1,6-and 3,6-quinones produced was greater than the 6,12-quinone with the P-450 3-MC and P-450 BNF but all three quinones were produced in low and equal amounts by the P-450 PB. In respect to the percent metabolites formed at a given region of the BP, P-450 3-MC and P-450 BNF preferred oxidation at the 1, 3 positions, 6 position and the 7, 8 positions, whereas the P-450 PB preferred oxidation at the 4, 5 position. This study demonstrates the unique positional specificity of different forms of cytochrome P-450 which may regulate the balance between activation and detoxification pathways of polycyclic aromatic hydrocarbon metabolism. (Author abstract) (28 Refs)

14. TEST-CONDITION-DEPENDENT INFLUENCE OF HARMAN AND NONHARMAN ON BENZO[A]PYRENE MUTAGENESIS IN SALMONELLA.

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Mutat Res; 104(1-3):9-15 1982

The influence of harman and norharman on benzo[a]pyrene [BaP] mutagenicity was examined under various experimental conditions in the Ames test to elucidate contradictory reports of mutagenic, co-mutagenic, and non-mutagenic activities of the compounds. Conditions varied were the nature and amount of metabolizing system (S9) preparation, amount of co-factors, and relative proportion of test chemicals. Harman and norharman were not mutagenic using this test system. Activation by 3-methylcholanthrene-, phenobarbital-, and Aroclor 1254-induced mouse liver homogenates led to decreased mutagenicity of BaP in Salmonella typhimurium TA98 upon addition of harman or norharman. Under conditions of activation by Aroclor 1254 induced rat liver homogenate, harman increased BaP revertants while norharman did not affect BaP mutagenicity. Using phenobarbital-induced mouse liver homogenate, varying the S9 extract amount, the amount of cofactors, or the relative proportions of test substances, within certain limits, had no effect on harman or norharman antagonism of BaP mutagenesis. While the Ames test is valuable in qualitatively determining mutagenicity/non-mutagenicity of single chemicals, different S9 extracts can yield widely varying results when assessing the possible synergistic or antagonistic effects of further chemicals. (8 Refs)

15. MODIFICATION OF BENZO[A]PYRENE-INDUCED TRANSFORMATION OF C3H/10T1/2 CELLS BY PREGNENOLONE-16ALPHA-CARBONITRILE AND DEXAMETHASONE.

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Cancer Lett; 15(3):215-221 1982

The effect of microsomal enzyme inducers, pregnenolone-16alpha-carbonitrile (PCN) and dexamethasone (DEX), on benzo[a]pyrene (BP)-induced transformation of C3H/10T1/2 cells is described. Data for benz[a]anthracene (BA) cytotoxicity and transformation which was used as a control, are presented. PCN increased the toxicity of BP and also increased the BP-induced transformation in a dose-dependent manner. Max enhancement of transformation occurred at 58 uM PCN and was 250% of the BP alone treated culture. DEX caused a dose-dependent reduction in BP-induced cellular transformation. Max reduction (65%) was observed at 23 uM DEX. DEX pretreatment also reduced the cytotoxic effect of BP. DEX treatment alone was not cytotoxic. The simultaneous treatment with DEX did abolish the toxic effect of BP, while PCN did not statistically alter BP toxicity. Both PCN and DEX only slightly induced aryl hydrocarbon hydroxylase (AHH) activity in the cells after a 24-hr treatment. The induction was maximal at approx 0.23 uM for DEX and 2.3 uM for PCN. The induction was much lower than that observed for BA. The greatest difference in metabolism of BP by pretreated C3H/10T1/2 cells occurred at 8-12 hr after the addition of BP. By 24 hr the amount metabolized in control and pretreated cells is nearly equivalent. Results suggest that a correlation between the ability of PCN and DEX to induce AHH activity or BP metabolism to water soluble products and their ability to alter transformation is not entirely consistent. (20 Refs)

16. SCREENING OF ANTIOXIDANTS AND OTHER COMPOUNDS FOR ANTIMUTAGENIC PROPERTIES TOWARDS BENZO[A]PYRENE-INDUCED MUTAGENICITY IN STRAIN TA98 OF SALMONELLA TYPHIMURIUM.

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Mutat Res; 101(2):99-114 1982

Mechanisms of antioxidant inhibition of carcinogenicity were studied by examining the effects of antioxidants on the oxidation of benzo[a]pyrene (BP) and its derivatives using the Salmonella typhimurium reversion test. The concentration ratio (compound/BP) was varied from 1-50 at a constant BP concentration of 8.2 nanomoles/ plate. Strong inhibitors were those which produced a greater than 25% inhibition of the mutagenicity of BP at concentrations no more than 5x the concentration of BP. According to this definition, disulfiram, phenothiazine, phenethyl isothiocyanate, phenyl isothiocyanate, and retinol were strong inhibitors. Weak inhibitors, producing greater than 25% inhibition at concentrations of no more than 50x the concentration of BP, included sodium selenite, polyvinylpyrrolidone, butylated hydroxytoluene (BHT), sodium diethyldisodium cyanate, and possibly butylated hydroxyanisole and ethoxyquin. Benzyl thiocyanate, ascorbic acid, glutathione, alpha-tocopherol, cysteamine, and sodium cyanate were not found to be inhibitors. Dose-response curves were obtained for the 17 most active compounds. Mechanisms of BP-induced mutagenicity are discussed. (67 Refs)

17. METABOLISM OF BENZO(A)PYRENE IN EPIDERMAL KERATINOCYTES AND DERMAL FIBROBLASTS OF HUMANS AND MICE WITH REFERENCE TO VARIATION AMONG SPECIES, INDIVIDUALS, AND CELL TYPES.

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Cancer Res; 42(5):1859-1865 1982

The metabolism of benzo(a)pyrene (BP) in epidermal keratinocytes and dermal fibroblasts of humans and mice was investigated with emphasis on variation among species, individuals, and cell types. Human epidermal and dermal cells were isolated from the skin of normal subjects followed by separation of the epidermis from the dermis with forceps. Metabolic activity of human epidermal cells on BP was consistently demonstrated by cell-mediated assay. Mutation of the V79 cells, measured as ouabain resistance, was induced in a dose-related fashion, although the extent of induced mutation varied from 5 to 22 ouabain-resistant colonies per 10(5) survivors/10 uM BP in cultures derived from different individuals. The most striking observation was that human dermal fibroblasts did not activate BP to a form that was mutagenic to cocultured V79 cells. This was observed without exception in all nine cultures of dermal fibroblasts and the one culture of embryo fibroblasts (IMR-90) tested. Analysis by high-pressure liquid chromatography indicated that human epidermal and dermal cells both metabolized BP, producing almost the whole series of known metabolites of BP. The amount of BP 7,8-dihydrodiol, a proximate metabolite of BP, produced by human dermal cells varied from 0.2 to 2.7% of the total BP added and seemed to be enough to induce mutation. Furthermore, human dermal cells not necessarily activated exogenously added BP 7,8-dihydrodiol to a form being mutagenic to V79 cells. These observations suggest that further metabolism of BP 7,8-dihydrodiol is partially or entirely blocked in human fibroblasts. In contrast to human fibroblasts, mouse fibroblasts isolated from the dermis of embryos did activate BP and induced mutation in cocultured V79 cells to a higher extent than did mouse epidermal cells, indicating interspecies variation in metabolic activation of BP between human and mouse fibroblasts. (26 Refs)

18. THE INFLUENCE OF VARIOUS ENZYME INDUCERS ON THE MICROSOMAL METABOLISM OF 7,8-BENZOFLAVONE.

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Carcinogenesis; 3(2):229-230 1982

Comparative in vitro metabolic experiments with 7,8-benzoflavone using microsomes prepared from the livers of control Sprague-Dawley rats or from rats of the same strain treated with phenobarbitone, 3-methylcholanthrene, or Aroclor 1254 (known inducers of hepatic cytochrome P450 mixed function oxidases) disclosed variable amounts of the three metabolites previously reported, namely the 5,6-epoxide, 9,10-dihydro-9,10-diol, and the 5 (or 6)-phenol. Microsomes from phenobarbitone-treated rats gave in addition a small amount of the 5,6-dihydro-5,6-diol, identified by mass spectrometry and uv spectroscopy. The apparent discrepancy between our previous results and those of Nesnow and Bergman is therefore partly resolved, although the absence of the 9,10-diol from their products remains unexplained, but may have resulted from their use of rats of a different strain. (Author abstract) (4 Refs)

19. THE METABOLISM OF PYRENE BY RAT LIVER MICROSOMES AND THE INFLUENCE OF VARIOUS MONO-OXYGENASE INDUCERS.

Jacob J, Grimmer G, Raab G, Schmoldt A
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Xenobiotica; 12(1):45-53 1982

Pyrene metabolite glc profiles were recorded and metabolites identified by mass spectrometry. Pyrene is metabolized by liver microsomes of untreated rats to 1-hydroxypyrene, 4,5-dihydroxy-4,5-dihydropyrene, two different diphenols and a triol, tentatively identified as 1,4,5-trihydroxy-4,5-dihydropyrene. Pretreatment with phenobarbital or polychlorinated biphenyls favors oxidation at the K-region, whereas cytochrome P-448 inducers stimulate oxidation at the non-K region of pyrene. 1-Hydroxypyrene does not inhibit pyrene oxidation. Pyrene diphenols are formed by secondary oxidation of 1-hydroxypyrene. Triols are formed from dihydrodiols by secondary oxidation. (Author abstract) (23 Refs)

20. STUDIES ON THE MECHANISMS INVOLVED IN MULTISTAGE CARCINOGENESIS IN MOUSE SKIN.

Slaga TJ, Fischer SM, Weeks CE, Klein-Szanto AJ, Reiners J
Biology Div., Oak Ridge Natl. Lab., Oak Ridge, TN, 37830
J Cel Biochem; 18(1):99-119 1982

Skin tumors can be induced in of mice by repeated applications of a carcinogen (complete carcinogenesis) or one subthreshold dose of a carcinogen followed by repeated applications of a weak or noncarcinogenic tumor promoter (initiation-promotion carcinogenesis). Of several mouse strains studied, Sencar was the most sensitive to both types of carcinogenesis. An important aspect of tumor initiation by polycyclic aromatic hydrocarbons (PAH) is their metabolism to an electrophilic intermediate(s) which interacts covalently with epidermal DNA. Tumor promotion can be divided into at least two stages: the first obtainable by limited treatment with 12-O-tetradecanoylphorbol-13-acetate (TPA) or certain nonpromoters; the second obtainable by repeated applications of mezerein. The dark basal keratinocytes (primitive stem cells) are important in the first stage of promotion. Most of the other cellular and biochemical events associated with promotion are actually associated with the second stage. Some evidence has been found suggesting that strain and/or stock differences in responses to complete and/or multistep carcinogenesis represent differences in responses to complete and/or promotion. Although C57BL/6 mice are relatively resistant to PAH initiation and phorbol ester promotion, they are fairly sensitive to complete carcinogenesis by PAH, suggesting that this strain is resistant to phorbol ester tumor promotion. Sencar and C57BL/6 mice seem to respond qualitatively but not quantitatively to one application of TPA. (97 Refs)

21. ROLE OF ISOZYMES OF CYTOCHROME P-450 IN THE METABOLISM OF N,N-DIMETHYL-4-AMINOAZOBENZENE IN THE RAT.

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Dept. Molecular Pharmacology, Albert Einstein Coll. Medicine, Bronx, NY, 10461
Drug Metab Dispos 10(2):102-109 1982

The metabolism of N,N-dimethyl-4-aminoazobenzene (DAB) was investigated in vitro by use of hepatic 10,000g supernatant fraction, microsomes, and purified cytochromes P-450 prepared from rats. Position-selective metabolism was studied in response to induction by 3-methylcholanthrene (MC), phenobarbital (PB), beta-naphthoflavone (BNF), and pregnenolone-16alpha-carbonitrile (PCN) as well as inhibition by SKF 525-A, metyrapone, alpha-naphthoflavone, and piperonyl butoxide. The principal Phase I pathways are demethylation of the tertiary (DAB) and secondary (MAB) amines and ring hydroxylation. When metabolism was measured with 10,000g supernatant fractions, each pathway responded differently and often independently to the inducers and inhibitors, suggesting that they are catalyzed preferentially by different isozymes of cytochrome P-450. Microsomes from PB-treated animals demethylated and hydroxylated DAB at the same rate as did control microsomes, based on cytochrome P-450 content, whereas microsomes from BNF- or MC-treated animals demethylated more rapidly and hydroxylated more slowly. Microsomes from PB-treated animals demethylated the secondary amine, MAB, more rapidly than the tertiary amine, DAB. Purified cytochrome P-448 from MC-treated animals catalyzed DAB demethylation very readily but hydroxylation very poorly. The turnover number was 10x that seen in microsomes from MC-treated animals. Only one of the four cytochrome P-450 fractions isolated from PB-treated animals had significant activity with DAB and the turnover number of one of these (fraction B) was approx that seen in microsomes. This study supports the concept of selectivity of various isozymes of cytochrome P-450 for the different steps in Phase I metabolism of DAB. Furthermore, it is apparent that the association of certain inhibitors with specific isozymes of cytochrome P-450 is a generalization that requires qualification in terms of the substrate(s) involved. (Author abstract) (49 Refs)

MUTAGENICITY OF ACTIVATED METABOLITES OF CARCINOGENS

22. SELECTIVE ACTIVATION OF SOME DIHYDRODIOLS OF SEVERAL POLYCYCLIC AROMATIC HYDROCARBONS TO MUTAGENIC PRODUCTS BY PROSTAGLANDIN SYNTHETASE.

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Cancer Res; 42(5):1620-1623 1982

The ability of prostaglandin synthetase (PGS) to cooxidize benzo(a)pyrene, benzo(a)anthracene, chrysene, and several of their dihydrodiol derivatives to mutagenic products was tested with Salmonella typhimurium strain TA98 and TA100. The microsomal fraction of ram seminal vesicles, a known source of PGS, in the presence of the PGS substrate arachidonic acid, metabolized benzo(a)pyrene-7,8-dihydrodiol, benzo(a)anthracene-3,4-dihydrodiol, and chrysene-1,2-dihydrodiol to mutagenic products. This activity was inhibited by the PGS inhibitor indomethacin. Unlike the PGS system, however, a cytochrome P-450-reduced nicotinamide adenine dinucleotide phosphate-dependent system, present in an Aroclor 1254-induced rat liver 9,000 x g supernatant fraction, also activated the parent compounds [benzo(a)pyrene, benzo(a)anthracene, chrysene] and several other benzo(a)anthracene dihydrodiols (the 1,2-dihydrodiol, the 8,9-dihydrodiol, and the 10,11-dihydrodiol). The chrysene trans-3,4, trans-5,6, and cis-5,6 diols were not activated to mutagens by either system. Thus, the PGS system appears to be more selective than does the cytochrome P-450 system in the activation of polycyclic aromatic hydrocarbons to mutagenic products, activating only those dihydrodiols with adjacent double bonds in the bay region from which the bay-region diol-epoxides are formed. (Author abstract) (20 Refs)

23. CELL-MEDIATED MUTAGENICITY IN CHINESE HAMSTER V79 CELLS OF DIBENZOPYRENES AND THEIR BAY-REGION FLUORINE-SUBSTITUTED DERIVATIVES.

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Cancer Res; 42(5):1646-1649 1982

The polycyclic aromatic hydrocarbons dibenzo(a,i)pyrene and dibenzo(a,h)pyrene, each of which possesses two bay regions, and their bay-region difluorinated derivatives were tested for mutagenicity for ouabain and 6-thioguanine resistance in Chinese hamster V79 cells. Since V79 cells do not metabolize polycyclic aromatic hydrocarbons, mutagenesis was tested in both the presence and the absence of golden hamster embryo cells capable of metabolizing polycyclic aromatic hydrocarbons. Neither of the dibenzopyrenes nor their fluorinated derivatives were mutagenic in the absence of the golden hamster embryo cells. In the presence of these cells (cell-mediated assay), both dibenzopyrenes were mutagenic, whereas the difluorinated derivatives, 2,10-difluorodibenzo(a,i)pyrene and 3,10-difluorodibenzo(a,h)pyrene, either were inactive or exhibited (on a dose basis) a weak response. However, the mutagenicity of the dibenzopyrenes was eliminated when they were coincubated with 7,8-benzoflavone, a mixed-function oxidase inhibitor. The results suggest that metabolic oxidation of these polycyclic aromatic hydrocarbons at the bay region (presumably to diol-epoxides) is required for a mutagenic response in the cell-mediated assay. (Author abstract) (39 Refs)

24. THE EFFECT OF LIVER POSTMITOCHONDRIAL FRACTION CONCENTRATION FROM AROCLOR 1254-TREATED RATS ON PROMUTAGEN ACTIVATION IN L5178Y CELLS.

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Mutat Res; 97(2):131-137 1982

Mouse L5178Y/TK +/- cells (strain 3.7.2C) were exposed to N-acetyl-2-aminofluorene (AAF: 50 or 67 ug/ml), 2-aminoanthracene (AA: 0.96 ug/ml), benzanthracene (BA: 7.35 ug/ml), benzo(a)pyrene (BP: 2.5 ug/ml), dimethylnitrosamine (DMN: 74.1 ug/ml), or 3-methylcholanthrene (MCA: 5.4 ug/ml), in the presence of varying concentrations (2.5-10%, vol/vol) of liver S9 postmitochondrial fraction from Aroclor-treated male CD rats. With AAF, AA, BA, BP, and MCA, the occurrence of trifluorothymidine-resistant mutants (TFTr) declined in proportion to increases in the S9 concentration during the 3-hr incubation period. With DMN, the occurrence of TFTr mutants increased moderately in proportion to increases in the S9 concentration during the 3-hr incubation period. The results suggest that two different metabolic events may be involved: activation via non-induced factors (perhaps enzymes) whose activities are totally dependent on the vol of S9 (DMN), and deactivation via induced detoxification pathways in a sequence favored by increasing the S9 concentration (the other promutagens tested). The use of a 'standard' concentration (10%) of rat liver S9 did not seem to provide optimal metabolic activation for any of the promutagens except DMN. With the other promutagens, the greatest degree of activation was observed at the lowest S9 concentration studied. (11 Refs)

25. THE USE OF PRIMARY RAT HEPATOCYTES IN ACHIEVE METABOLIC ACTIVATION OF PROMUTAGENS IN THE CHINESE HAMSTER OVARY/HYPOXANTHINE-GUANINE PHOSPHORIBOSYL TRANSFERASE MUTATIONAL ASSAY.

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Environ Mutagen; 4(1):55-64 1982

Details are presented of a method used to evaluate the use of primary rat hepatocyte-mediated mutagenicity with the use of the Chinese hamster ovary (CHO)/hypoxanthine-guanine phosphoribosyl transferase mutational assay. Aflatoxin B1 (AFB1), 7,12-dimethylbenz(a)anthracene (DMBA), and benzo(a)pyrene produced increases in mutant fractions of treated CHO cells as a function of concentration. The time required for optimum expression of mutant phenotype was approx 8 days after exposure to DMBA and AFB1. (35 Refs)

26. DIFFERENCES IN TEMPORAL ASPECTS OF MUTAGENESIS AND CYTOTOXICITY IN CHINESE HAMSTER CELLS TREATED WITH METHYLATING AGENTS AND THYMIDINE.

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Proc Natl Acad Sci USA; 79(5):1643-1647 1982

Equitoxic concentrations of N-methyl N'-nitro-N-nitrosoguanidine (MNNG) and methyl methanesulfonate (MeMes) produced different frequencies of 5-azaguanine-resistant mutants and different amounts of N7-methylguanine, O6-methylguanine (m6G), and N3-methyladenine in the DNA of V79

Chinese hamster cells. Thus, neither the cytotoxicities nor the mutagenicities of these methylating agents could be attributed solely to nitrogen or to oxygen methylations in the DNA. However, MNNG produced 12-fold more m6G and 5-fold more mutants than did MeMes, indicating that a substantial part of the MNNG-induced mutations resulted from m6G-thymine mispairing during DNA replication. The expression as mutants of mutagenic oxygen methylations in the DNA of cells treated with MNNG was enhanced by thymidine (dThd) and deoxycytidine (dCyd), but these nucleosides did not significantly enhance MeMes-induced mutagenesis. The cytotoxicities of MNNG and MeMes were also increased by 10 uM dThd in proportion to the amount of m6G in the DNA. These increases in cytotoxicity were abolished by dCyd, which did not greatly reduce the dThd-induced enhancements of mutagenesis. Moreover, when dThd was present only during the 2-hr treatment with MNNG, maximal cytotoxicity occurred, but MNNG-induced mutagenesis was not increased. Maximal mutagenesis occurred when the dThd was present throughout the first doubling time of the MNNG-treated cells. Thus, the expression of the cytotoxicity and the mutagenicity associated with m6G in the DNA of V79 cells occurred by quite different mechanisms. (Author abstract) (31 Refs)

27. CYTOTOXICITY AND MUTAGENICITY OF DIMETHYLNITROSAMINE IN MAMMALIAN CELLS (CHO/HGPRT SYSTEM): ENHANCEMENT BY CALCIUM PHOSPHATE.

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Environ Mutagen; 4(1):7-18 1982

Conditions for use of the metabolic activator, S9, in Chinese hamster ovary (CHO) cells were studied in the hypoxanthine-guanine phosphoribosyl transferase system to quantify the mutagenicity of dimethylnitrosamine (DMN). The S9 protein was obtained from liver of Aroclor 1254-induced Sprague-Dawley rats. DMN (5 mg/ml) added to cultures of CHO cells, increased both cytotoxicity and mutagenicity with addition of S9, and each increased with increasing amounts of S9; without S9 there was no activity. A previous observation that CaCl2 led to increased cytotoxicity and mutagenicity was verified by addition to the incubation mixture of 10 milliM (mM) MgCl2, 10 mM CaCl2, or both. The greatest increase in activity was observed when both CaCl2 and MgCl2 were included. A precipitate was formed in both the S9 mix and the incubation medium at all concentrations of CaCl2, which resulted in increased activity of DMN (ie, 2.5-10 mM). Since formation of a calcium phosphate precipitate seemed the most likely explanation, the effect of added sodium phosphate was investigated. Maximum activity was obtained with addition of 50 mM sodium phosphate in addition to 10 mM CaCl2 and 10 mM MgCl2. DMN activity increased with increased amounts of S9 protein over the range 0.3-3.0 mg/ml in the S9 mix. The mutagenicity of DMN can be described as 110 mutants/10(6) cells per mM DMN per mg/ml S9 protein per hour. (20 Refs)

28. SUPERMUTAGENICITY OF ETHYLNITROSOUREA IN THE MOUSE SPOT TEST: COMPARISONS WITH METHYLNITROSOUREA AND ETHYLNITROSOURETHANE.

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Mutat Res; 92(1/2):193-204 1982

The embryotoxicities and mutagenicities of ethylnitrosourea (ENU: 25-100 mg/kg), methylnitrosourea (MNU: 5-7.5 mg/kg), and ethylnitrosourethane (NEC: 100-150 mg/kg) were studied in (C57BL/R1 x multiple-recessive T)F1 mice. Female C57BL/R1 mice were treated with the agent on day 9 or 10 of pregnancy. The spot test was used to obtain information on mutations, cytotoxicity (the occurrence of white midventral spots during the first 7 wk after birth), and teratogenic effects. For all endpoints studied, ENU was more effective than NEC. Compared to MNU, ENU was less toxic, less teratogenic, and less mutagenic in the spot test but more mutagenic in spermatogonia and a much stronger transplacental carcinogen than MNU. MNU is apparently a stronger inducer a gross chromosomal damage than ENU, whereas ENU causes more gene mutations than MNU. Both types of mutational damage are evident on the spot test; gene mutations are evident from spermatogonial studies. (20 Refs)

29. SHORT-TERM TESTS FOR TRANSPLACENTALLY ACTIVE CARCINOGENS. SENSITIVITY OF THE TRANSPLACENTAL MICRONUCLEUS TEST TO DIETHYLNITROSAMINE.

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Mutat Res; 104(1-3):165-171 1982

Dose-dependent clastogenic effects of diethylnitrosamine (DEN) in utero were examined using the transplacental micronucleus test. Random-bred albino mice were mated and treated with DEN ip. Frequencies of polychromatic RBC containing micronuclei were determined in preparations of fetal liver and neonatal peripheral blood. The youngest animals investigated were exposed to DEN in utero during days 15-16 of gestation. A small but significant increase in frequency of micronucleated polychromatic RBC (MNPCE) was detectable in fetal liver 36 hr after treatment. A high level of significance was obtained when exposure was initiated during day 17 of gestation. No increases in frequency of MNPCE were observed in maternal bone marrow. Polychromatic RBC derived from fetal liver during the last day of gestation persisted in the circulation of neonatal animals. Therefore, the frequency of MNPCE in smears of peripheral blood can be used to measure clastogenic effects when the metabolic capacity of the prenatal liver is fully expressed. Pregnant animals were treated late on day 17 of gestation and blood smears were prepared from newborn animals 45 hr after beginning exposure. Dose-related increases in frequencies of MNPCE in neonatal mice after in utero exposure were obtained. Variation in response to DEN between members of litters and between litters was greater than observed with other chemicals, suggesting that onset of the ability to metabolize DEN is variable. (28 Refs)

30. MUTAGENICITY AND ALPHA-HYDROXYLATION OF N-NITROSOPYRROLIDINE AND N-NITROSOPIPERIDINE: A POSSIBLE CORRELATION.

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Toxicology; 22(4):345-352 1982

The rate of biotransformation of N-nitrosopyrrolidine (NPyrr) and N-nitrosopiperidine (NPip) into 1,4-butanediol (BTD) and 1,5-pentanediol (PTD), respectively, in the presence of liver post-mitochondrial fractions was investigated Postmitochondrial fractions (S9) were obtained from homogenized rat livers and incubated with the test material. NPyrr and NPip metabolites were determined by gas chromatography. The rates of biotransformation of NPyrr and NPip were optimal after 2 hr. The quantity of BTD produced was positively correlated with the concentration of NPyrr (0-10 umole/0.1 ml) in the mixture. BTD concentrations detected in the presence of a sensitive Salmonella strain was lower, but still positively correlated with NPyrr concentration. Both mutagenicity and metabolism of NPYrr were related to the concentration of S^9 liver fractions and required the presence of disodium salt (NADP). With NPip a similar correlation was observed between the mutagenic activity and dose of PTD undetected in the presence of sensitive Salmonella. The metabolic mechanism for NPyrr and NPip is apparently an NADPH-dependent alpha-hydroxylation by which the cyclic nitrosamines were converted into mutagenic intermediates. (12 Refs)

31. INDUCTION OF SISTER-CHROMATID EXCHANGES BY INDIRECT MUTAGENS/CARCINOGENS IN CULTURED RAT HEPATOMA AND ESOPHAGEAL TUMOR CELLS AND IN CHINESE HAMSTER DON CELLS CO-CULTIVATED WITH RAT CELLS.

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Mutat Res; 93(2):409-418 1982

The inducibility of sister-chromatid exchanges (SCEs) in rat ascites hepatoma (AH66-B) and a rat esophageal tumor (R1) cell lines by 2-acetylaminofluorene, butylbutanolnitrosamine, cyclophosphamide, urethane, 4-aminoazobenzene, 2-methyl-4-dimethylaminoazobenzene, 3'-methyl-4-dimethylaminoazobenzene, 4-o-tolyazo-o-toluidine, benzo(a)pyrene, 7,12-dimethylbenzyl(a)anthracene, 3-methylcholanthrene, and diethylstilbestrol (DES) was studied. Six of the chemicals were used with a cell-mediated system using Chinese hamster Don-6 cells as the target cells and co-cultivated AH66-B or R1 cells as the metabolizing feeder layer. Out of 14 indirect mutagens/carcinogens tested, 11, including 5 amine derivatives, 3 azo compounds, 2 aromatic hydrocarbons and 1 steroid, induced SCEs in AH66-B and/or R1 cells. The frequency of SCEs in Don-67 cells exposed to 6 selected chemicals was substantially enhanced in the presence of AH66-B or R1 cells. For some chemicals, especially aromatic hydrocarbons, the doses required to induce SCEs in AH66-B and R1 cells were much higher than those reported for some other cell systems. Certain chemicals, eg, DES, were active inducers of SCEs in the present systems, but are known to be inactive in microbial and other test systems. The two approaches described represent simple and reliable screening assays in vitro for detection of indirect mutagens/carcinogens. (32 Refs)

32. MUTAGENICITY AND TOXICITY OF AFLATOXIN PRECURSORS.

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Environ Mutagen; 4(1):19-26 1982

The Salmonella/microsome test and chick embryo test were used to determine the toxicity and mutagenicity of five aflatoxin B1 (AFB1) precursors: norsolorinic acid, averantin, averufin, versicolorin A and sterigmatocystin. A definite pattern emerged which indicated that the nearer to AFB1 an intermediate appears in the biosynthetic pathway, the greater is its mutagenicity and toxicity. (19 Refs)

33. MUTAGENICITY OF N-HYDROXY-2-ACETYLAMINOFLUORENE AND N-HYDROXYPHENACETIN AND THEIR RESPECTIVE DEACETYLATED METABOLITES IN NITROREDUCTASE DEFICIENT SALMONELLA TA98FR AND TA100FR.

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Carcinogenesis; 3(2):167-170 1982

The mutagenicity of N-hydroxy-2-acetylaminofluorene and N-hydroxyphenacetin and their respective deacetylated metabolites, N-hydroxy-2-aminofluorene and 2-nitrosofluorene, and N-hydroxyphenetidine and p-nitrosophenetole was determined in nitroreductase deficient Salmonella tester strains TA98FR and TA100FR. The mutagenicity of N-hydroxy-2-acetylaminofluorene mediated by either rat liver microsomes or rat liver 105,000 g supernatant fractions was no different in either TA98 (nitroreductase proficient) or TA98FR (nitroreductase deficient). Similarly the mutagenicity of N-hydroxyphenacetin mediated by hamster liver microsomes was not affected by either the presence or absence of nitroreductase activity in TA100. N-Hydroxy-2-aminofluorene and 2-nitrosofluorene were equipotent direct acting mutagens in both TA98 and TA98FR, as were both N-hydroxyphenetidine and p-nitrosophenetole in TA100 and TA100FR. Ascorbate (5 mM) and NADPH (1 mM) had no significant effect on the mutagenicity of either N-hydroxy-2-acetylaminofluorene, N-hydroxy-2-aminofluorene, or 2-nitrosofluorene in TA98 or TA98FR whereas ascorbate and NADPH markedly inhibited the mutagenicity of both N-hydroxyphenetidine and p-nitrosophenetole in both TA100 and TA100FR. Ascorbate appears to be inhibiting the mutagenicity of N-hydroxyphenetidine and p-nitrosophenetole as a result of the nonenzymatic chemical reduction of these compounds to non-mutagenic derivatives. (Author abstract) (15 Refs)

34. SELECTIVE DEACTIVATION OF ICR MUTAGENS AS RELATED TO THEIR DISTINCTIVE PULMONARY CARCINOGENICITY.

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Carcinogenesis; 3(2):187-194 1982

The mutagenicity patterns and the metabolic behavior of four structurally related ICR compounds were investigated using the Salmonella/microsome test. ICR 191 and ICR 170 reverted four his strains (TA1537 greater than TA100 greater than TA98 and TA1538), while ICR 191-OH and ICR 170-OH reverted TA1537 only, with a narrow range of mutagenic activity. Although all the products tested were shown to contain a common mutagenic impurity, analysis of chemicals fractionated by hplc provided evidence that pure ICR 191-OH and ICR 170-OH also induce frameshift errors. The mutagenic activity of all the four ICR compounds, as well as of their common impurity, was decreased in the presence of S-9 mix containing rat liver S-9 fractions, a trend confirmed by hplc of ICR/S-9 mixtures. Despite the greater mutagenic potency in the absence of metabolic systems, ICR 191 was deactivated far more efficiently and rapidly than ICR 170 by a variety of mouse (liver greater than lung) and rat (liver greater than testis greater than kidney greater than lung greater than striated muscle greater than spleen) S-9 fractions. Mouse preparations were more effective than the corresponding rat preparations. Aroclor 1254 strongly stimulated the activity of the NADPH-requiring enzymes responsible for ICR deactivation. Hplc analyses ruled out interconversion among the four ICR compounds in the presence of liver S-9 fractions, while revealing the appearance of new distinct peaks for ICR 191, ICR 170 and ICR 170-OH. The selective metabolic deactivation of ICR compounds may be related to the findings of previous carcinogenicity studies which showed the induction of lung adenomas following iv but not ip administration of ICR 170. Conversely, ICR 191 and ICR 191-OH showed no activity even when administered iv. Since intercalation of ICR compounds into DNA is the molecular basis for both mutagenic and antitumor activities, their distinctive metabolic reactivity may be also responsible for the differential efficacy in pharmacological assays. (Author abstract) (27 Refs)

35. COMPARISON OF THE MUTAGENICITIES OF 4-AMINOBIPHENYL AND BENZIDINE IN THE SALMONELLA/MICROSOME, SALMONELLA/HEPATOCYTE AND HOST-MEDIATED ASSAYS.

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Mutat Res, 93(2):317-325 1982

The mutagenicity of two structurally related carcinogenic aryl amines, 4-aminobiphenyl (4-AB) and benzidine (BZ), which are subject to a complex in vivo metabolism, was studied by three different test methods. The Salmonella/microsome (S/m) assay was performed by the Ames method with strains TA1538 and TA100 of Salmonella typhimurium. In the Salmonella intrasanguineous assay male Wistar rats (200 g) were injected in the lateral tail vein with 1 ml of saline suspension of S typhimurium, followed by ip injection of either 4-AB or BZ. Revertants in bacteria grown from liver suspensions were counted. The Salmonella/hepatocyte (S/h) assay involved counting of revertant colonies after plating from an incubation mixture containing rat liver hepatocytes, S typhimurium, and mutagen incubated at 37 C for 1 hr. The mutagenicity of the two compounds varied depending upon whether metabolic inactivation was carried on in vivo or by S9 mix in the Ames test. The results obtained for both compounds in the S/h assay resembled more closely those of the host-mediated assay than they did the results of the S/m assay. (16 Refs)

36. GENOTOXIC ACTIVITY OF FIVE ANTIDEPRESSANT HYDRAZINES IN A BATTERY OF IN VIVO AND IN VITRO SHORT TERM TESTS.

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J Toxicol Environ Health; 9(2):287-303 1982

The mutagenic and potential carcinogenic activity of iproniazid (IPZ), phenelzine (PHZ), nialamide (NLM), isocarboxazid (ICB), and mebanazine (MBZ) was assessed. Mouse liver and lung DNA damage was analyzed by the alkaline elution technique after single or daily, ip or po doses of each drug, ranging from 0.333 to 2x the LD50. ICB, NLM, PHZ, and MBZ caused significant DNA fragmentation with decreasing efficiency, while IPZ was ineffective. In contrast to ICB, NLM, and PHZ, MBZ induced DNA damage only in the lung and only after five successive daily doses. Sister chromatid exchange (SCE) in mouse bone marrow cells was assessed after ip administration of 1-2x the LD50 of each drug except MBZ. SCE frequencies in the IPZ, NLM, ISB, and PHZ treated groups increased 71%, 49%, 46%, and 34%, respectively, when compared with control groups. A dose-dependent increase in SCE frequency was observed in mice treated with ICB at LD50 and 2x LD50. Mutagenic activity was investigated with the Salmonella/microsome test. NLM and PHZ were mutagenic in the spot test (1 mg/plate) and the plate incorporation test (PIT). ICB and IPZ were not mutagenic, and MBZ was weakly mutagenic in the PIT. Antibacterial activity in repair deficient Escherichia coli was also assessed for each compound. ICB and IPZ were scarcely toxic, while NLM, PHZ, and MBZ showed significantly increased antibacterial activity in some E coli strains with spot and spiral tests. Long term carcinogenic tests should be performed for NLM and ICB, which are still in clinical use. (30 Refs)

37. ANALYSIS OF A METHOD FOR TESTING AZO DYES FOR MUTAGENIC ACTIVITY IN SALMONELLA TYPHIMURIUM IN THE PRESENCE OF FLAVIN MONONUCLEOTIDE AND HAMSTER LIVER S9.

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Mutat Res; 97(2):103-116 1982

A protocol was developed for assessing the mutagenicity of azo dyes derived from mutagenic or potentially mutagenic aromatic amines in Salmonella typhimurium TA98. In the protocol, uninduced hamster liver S9 (150 ul) is used instead of Aroclor 1254-induced rat liver S9 (max, 50 ul) in the standard assay; flavin mononucleotide is used instead of riboflavin to reduce the azo compounds to free amines; the cofactor mix is modified to include exogenous glucose 6-phosphate dehydrogenase, NADPH, and 4x the standard amount of glucose-6-phosphate; and 30 min of preincubation is performed before the top agar is added. All of the modifications were necessary for optimal mutagenic activity of the azo dyes tested: Congo red (CR), benzopurpurine 4B (BP4B), trypan blue (TB), and Direct Blue 1 (DB1). The assay was also performed using known or probable reduction products of the dyes having known mutagenic and carcinogenic activity: benzidine (BZD; a reduction product of CR), o-tolidine (o-TD: a reduction product of BP4B and TB), and o-dianisidine (o-DAD: a suspected reduction product of DB1). The mutagenicities of CR, TB, and DB1 were greater when hamster liver S9 was substituted for rat liver S9. BZD was more mutagenic with hamster liver S9 than with rat liver S9, but o-TD and o-DAD were not. Rat liver S9 inhibited the ability of hamster liver S9 to activate BZD to a mutagen. The presence in rat liver S9 of an inhibitor of BZD metabolic activation may account for the failure of BZD and a BZD dye (CR) to be strongly mutagenic in the presence of rat liver S9. (27 Refs)

38. MUTAGENICITY OF SUBSTITUTED CARBAZOLES IN SALMONELLA TYPHIMURIUM.

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Mutat Res; 101(2):141-150 1982

Mutagenic activities of several substituted carbazoles in Salmonella typhimurium TA1535, TA1537, TA 1538, TA98, and TA100 were compared. Of all possible isomers of methylcarbazole, only 9-methylcarbazole was mutagenic when assayed in S typhimurium TA100 in the presence of S9. Other dimethylcarbazoles in which one of the methyl substituents was in the 9-position were similarly assayed for mutagenic activity; with the exception of 1,9-dimethylcarbazole, each of the compounds were mutagenic in TA100 with activation. The mutagenic potency of the dimethylcarbazoles was less than that of 9-methylcarbazole. All of the carbazole derivatives were inactive as mutagens in TA1535, TA1537, TA1538, and TA98, with or without S9 mix. Substitution at the 9-position of carbazole resulted in a loss of mutagenic activity. Metabolism studies performed with 9-methylcarbazole confirmed that 9-hydroxymethylcarbazole is a major metabolite and proximate mutagen. It was suggested that the mutagenicity of 9-hydroxymethylcarbazole is related to the release of formaldehyde, a hypothesis supported by the lack of mutagenic activity of 9-formylcarbazole and 9-acetylcarbazole. (17 Refs)

39. THE CHEMICAL ACTIVATION OF NON-MUTAGENIC NITRATED POLYCYCLIC AROMATIC HYDROCARBONS TO MUTAGENS.

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Mutat Res, 92(1/2):29-37 1982

Ames assays in Salmonella strains TA1535, TA100, TA98, and nitroreductase (NRase)-deficient strains TA100NR and TA98NR were performed with 5-nitroquinoline (5-NQ), 6-nitroquinoline (6-NQ), 8-nitroquinoline (8-NQ), 1,8-dinitronaphthalene (1,8-DNN), 1-5-dinitronaphthalene, 4-nitroquinoline 1-oxide, 2-nitrofluorene, and nitrofurantoin, in the presence or absence or rat liver microsomes (S9 mix). Both 5-NQ and 6-NQ were direct-acting bacterial mutagens, but 8-NQ (a carcinogen in rats) and 1,5-DNN (an analog of 8-NQ) were not mutagenic even in the presence of S9 mix. The non-mutagenicity of 8-NQ and 1,8-DNN could be overcome chemically, in situ, by the addition of zinc (Zn) dust. Anaerobic conditions were not required for a max yield of the mutagenic product of 1,8-DNN The mutagenicity of the 1,8-DNN product was not due to a nitro function, as shown by the fact that it was fully active even in the NRase-deficient strain TA100NR. It is concluded that although bacteria can reduce some nitrated polycyclic aromatic hydrocarbons (N-PAH) to mutagens, their NRases cannot reduce the nitro functions of all N-PAHs to the proximate mutagenic hydroxylamines. Chemical reduction of the N-PAH (ie. non-enzymatic activation) with Zn (which is compatible with the Ames bioassay) may be a useful addition to the procedure in the evaluation of the potential mutagenicity of nitro-containing chemicals. (24 Refs)

40. GENETIC TOXICOLOGY STUDIES WITH 2-NITROBENZOFURANS AND 2-NITRONAPHTHOFURANS.

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Mutat Res; 104(1-3):1-8 1982

The mutagenic activity of three 2-nitronaphtho[2,1-b]furans two 2-nitronaphtho[3,2-b]furans, and two 2-nitronaphtho[1,2-b]furans was tested using the Salmonella/microsome assay (Mutatest). The seven compounds gave a mutagenic response with the following characteristics: it occurs on strains TA1537, TA1538, TA98, and TA100, but not no strain TA1535; the mutagenic response is partially dependent on the bacterial nitroreductase activity and is lower in the presence of an activating mixture S9 from rat liver; it varies quantitatively and qualitatively with the structure of the compound. The mutagenic responses of the 2-nitronaphthofurans and three 2-nitrobenzofurans was also examined in a phage-induction assay (Inductest). The mutagenic potency measured in the Mutatest correlated well with that measured by the Inductest; those compounds which were negative in the Mutatest were also negative in the Inductest. The mutagenic activity of the two most potent mutagens examined was tested using strains TA1978 and TA2421, the UVr+ counterparts of the TA1538 and TA98 uvrB excision-repair mutants used in the Mutatest. The mutagenic response was reduced by at least a factor of 100 compared to the uvrB mutants, indicating that the excision-repair system is efficient in preventing the mutagenic effect of the 2-nitronaphthofurans. 2-Nitro-7-methoxynaphtho[2,1-b]furan (R7000), one of the most potent compounds, also induced sperm abnormality in mice (Spermatest). The results of the bacterial tests and Spermatest in relation to the possible genetic toxicity of these compounds is discussed. (11 Refs)

41. CONTRIBUTION OF 1-NITROPYRENE TO DIRECT-ACTING AMES ASSAY MUTAGENICITIES OF DIESEL PARTICULATE EXTRACTS.

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Mutat Res; 104(1-3):17-23 1982

The percentage contribution [P] of 1-nitropyrene [1-NP], a derivative of the carcinogenic polycyclic aromatic hydrocarbons, to the direct-acting Ames Salmonella assay mutagenicities of extracts of exhaust particles collected from three different diesel powered vehicles was assessed. 1-NP was shown to be a substantial contributor to the Ames assay mutagenicities for the three diesel particulate extracts examined. For Salmonella strains TA98, TA100, and TA1538, respectively, P was 16, approx 1, and 7% for one vehicle (1-NP = 2,030 +-220 ppm); 24, 9, and 17% for the second vehicle (1-NP = 150 +-30 ppm), and 13, 4, and 13% for the third vehicle (1-NP = 55 +-11 ppm). Using this assay system, even a 1% contribution of a single compound is important, considering the several hundreds of compounds present in the particulate extracts. Salmonella-histidine reversion assays indicated that the extract matrix had little effect on the mutagenicity of 1-NP. The significance of diesel exhaust-associated 1-NP in relation to adverse effects on human health was discussed. (22 Refs)

42. MUTAGENICITY OF NIFURPIRINOL (P-7138) IN ESCHERICHIA COLI WP2 AND SALMONELLA TYPHIMURIUM TA100.

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Mutat Res; 104(1-3):61-66 1982

The mutagenicity of nifurpirinol (NP) was examined using UV-repair-competent and deficient strains of Escherichia coli B/r WP2 and the Salmonella typhimurium strain TA100 in the absence of rat microsomal activation system (S9 mix). The modified Ames test with S typhimurium TA100 was used to compare mutagenic activities of NP in the presence and absence of S9 mix and to study changes in mutagenicity after exposing NP to sunlight. Potent, dose-related mutagenic effects and susceptibility to photodegradation are reported. (8 Refs)

43. MUTAGENICITY OF CHLOROALKENE EPOXIDES IN BACTERIAL SYSTEMS.

Kline SA, McCoy EC, Rosenkranz HS, Van Duuren BL
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Mutat Res; 101(2):115-125 1982

Epoxides of six chloro-olefins, cis-1-chloropropene oxide (1), trans-1-chloropropene oxide (2), cis-1,3-dichloropropene oxide (3), trans-1,3-dichloropropene oxide (4), trichloroethylene (5) and tetrachloroethylene oxide (6), were examined for mutagenicity in Salmonella typhimurium TA 1535 and Escherichia coli WP2 uvrA and for genotoxicity in E coli pol A-/pol A+ DNA repair assay in the absence of metabolic activation. In mutagenicity tests, the compounds (CPD) generally exhibited toxicity. However, at lower doses, concentration-dependent mutagenic responses in Salmonella TA1535 were obtained for all chemicals except for CPD 5. Similar results were obtained with E coli WP2 uvrA except that neither CPD 5 nor 6 were mutagenic. CPD 3 and 4 showed the highest specific mutagenicities. Both CPD 4 and its aqueous decomposition product exhibited dose-dependent mutagenicity, although the unhydrolyzed form was 2-6x more potent. In genotoxicity tests, CPD 1, 2, 3, and 4 were mutagenic for S typhimurium TA1535 and for E coli WP2 uvrA and differentially inhibited the E coli DNA repair-deficient strain. CPD 5 was not mutagenic for Salmonella and E coli WP2 uvrA, but exhibited DNA-modifying activity. CPD 6, while non-mutagenic for E coli WP2 uvrA, was mutagenic for Salmonella, and positive in the E coli pol A1-assay. CPD 3 and 4 exhibited the highest potencies in all the systems studied. The results indicated that alpha-chloroepoxides of biologically active halo-olefins are themselves biologically active in the absence of metabolic activation. (38 Refs)

44. MUTAGENICITY STUDIES WITH 2,4,5-T ON BACTERIA AND MAMMALIAN GERM CELLS.

Herbold BA, Machemer L, Rohrborn G
Inst. Toxicology, Bayer AG, Friedrich Ebert Strasse 217-219, D-5600 Wuppertal 1, W. Germany
Teratogenesis Carcinog Mutagen; 2(1):91-101 1982

The herbicide 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) was tested for mutagenicity in an Ames mutagenicity with microsomal activation. a dominant lethal test in rats, and a cytogenetic assay of Chinese hamster spermatogonia. The 2,4,5-T contained 0.05 ppm dioxin. Salmonella strains used were TA 98, 100, 1535, and 1537, with cyclophosphamide and trypaflavine as controls. 2,4,5-T was tested at 4-2,500 ug/plate. In the dominant lethal test rats were fed 0.1, 1, or 100 mg/kg 2,4,5-T for 8 wk and then mated. Corpora lutea, dead, and viable embryos were counted 12 days after mating, and the rate of dominant lethal mutations determined. For the cytogenetic assay male Chinese hamsters were fed 0, 0.5, 5, or 50 mg/kg 2,4,5-T per day for 5 days in one test, and 0 and 500 mg/kg on the same schedule in a second test. The 2,4,5-T was not mutagenic in any of these tests. These findings are compared with tests of 2,4,5-T in other systems. (46 Refs)

45. AN EVALUATION OF THE GENOTOXIC PROPERTIES OF INSECTICIDES FOLLOWING PLANT AND ANIMAL ACTIVATION.

Gentile JM, Gentile GJ, Bultman J, Sechreist R, Wagner ED, Plewa MJ
Dept. Biology, Hope Coll., Holland, MI, 49423
Mutat Res; 101(1):19-29 1982

Commercial grades (CG) and technical grades (TG) of two carbamate, six organophosphate, and two chlorinated hydrocarbon insecticides were tested for genotoxicity in Salmonella typhimurium and Saccharomyces cerevisiae with rat liver metabolic activation (S9), plant metabolic activation (maize 1S fractions), or no activation. CG of each insecticide was also tested for mutations at the waxy (wx) locus of Zea mays. Carbofuran, metham, curacron, phorate and chlorpyrifos were negative in all assays. CG and TG fonofos were mutagenic to Salmonella following S9 activation and TG fonofos was weakly positive in the S cerevisiae assay. TG terbufos was recombinogenic in S cerevisiae both directly and with S9 activation, while CG was weakly recombinogenic when tested directly. Field formulation of ethoprop was mutagenic in the maize wx assay. TG heptachlor was mutagenic to Salmonella with S9 activation. Both CG and TG chlordane were recombinogenic to Saccharomyces following S9 activation. Both heptachlor and chlordane were genotoxic following 1S activation and both were mutagenic in the maize wx assay. Mammalian microsomal activation systems should be complemented with plant activation systems in order to provide a comprehensive analysis of the genotoxic potential of agricultural agents. (26 Refs)

46. STUDIES ON THE MUTAGENIC POTENTIAL OF THE PESTICIDE CHLORDIMEFORME AND ITS PRINCIPAL METABOLITES IN THE MOUSE HERITABLE TRANSLOCATION ASSAY.

Lang R, Adler ID
Res. Lab., Schering, Berlin/Bergkamen, W. Germany
Mutat Res; 92(1/2):243-248 1982

Random-bred NMRI/SPF male mice were treated for 7 wk (by gavage) with max tolerated doses of chlordimeforme (CDMF: 120 mg/kg/day) or one of its principal metabolites, N-formyl-4-chloro-o-toluidine (100 mg/kg/day) and 4-chloro-o-toluidine (200 mg/kg/day), then mated with untreated females. The treated mice and male F1 offspring were screened for fertility. Animals showing reduced fertility or sterility were examined cytogenetically, by scoring meiotic chromosomes for translocation multivalents or assessing mitotic cells for marker chromosomes. CDMF and both of its principal metabolites at toxic doses did not induce translocation heterozygosity. The positive control agent, triethylene melamine (0.05 mg/kg/day), gave the expected mutagenic response. (7 Refs)

47. STRUCTURE-MUTAGENICITY RELATIONSHIP IN ALPHA,BETA-UNSATURATED CARBONYLIC COMPOUNDS AND THEIR CORRESPONDING ALLYLIC ALCOHOLS.

Lutz D, Eder E, Neudecker T, Henschler D
Inst. Toxicology, Univ. Wurzburg, Versbacher Str. 9, D-87 Wurzburg, W. Germany
Mutat Res; 93(2):305-315 1982

The mutagenicities of 16 allylic alcohols and their carbonylic derivatives commonly used in industry were determined using the Ames test with Salmonella typhimurium TA100 in the modified suspension test of Rannug et al. Of the alcohols, allyl alcohol proved to be a potent mutagen (750 revertants/umole without S9 mix; 145 revertants/umole with S9); the next higher homolog and two isomers showed little or no mutagenic effect. Glycidol, the epoxide of allyl alcohol was distinctly mutagenic, but much less so than the non-epoxidized alcohol. Acrolein, crotonaldehyde, 2-methylacrolein, and methylvinyl ketone were strongly mutagenic without S9 mix; all but acrolein were also distinctly mutagenic with S9 mix. 2-cyclohexene-1-one was slightly mutagenic; cinnamylaldehyde and citral were not at all mutagenic according to the modified Ames test. In general mutagenicity was highest in the lowest members of homologous series, both of allylic alcohols and their corresponding unsaturated carbonyl compounds. There was a positive correlation between electrophilicity and direct mutagenicity. S9 mix did not increase mutagenicity in non-mutagenic compounds, but more or less inactivated the mutagenic compounds depending on their electrophilic properties. (23 Refs)

48. CLASTOGENIC ACTIVITY OF BILE ACIDS AND ORGANIC ACID FRACTIONS OF HUMAN FECES.

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Naylor Dana Inst. for Disease Prevention, American Health Foundation, 1 Dana Road, Valhalla, NY, 10595
Cancer Lett; 15(3):317-327 1982

Clastogenic activity in bile acids and in the acid fractions (AF) of saponified chloroform-methanol extracts (CME) from human fecal matter (FM) is reported. AF of saponified CME from four human donors were studied. With AF of FM from subjects A and B, frequencies of aberrant metaphases and exchanges were considerably higher than those for the control. The C and D AF also brought about a slight elevation in aberrations. The addition of S9 mix did not enhance the clastogenic activities of AF. With hexane extracts, no detectable increase in frequency of chromosome aberrations above control values were observed, either with or without the addition of S9 mix. When five of the major bile acids were assayed, cholic acid induced a slight increase in aberration frequency and ursodeoxycholic acid (UDCA) a much larger one. Addition of S9 enhanced the increase, but the presence of S9 was not a necessary condition for the demonstration of clastogenic activity. S9 also decreased the concentration of bile acid necessary to produce chromosome damage. Experiments using the standard S9 mix containing all cofactors, the standard S9 mix without NADPH, and an S9 mix with all cofactors in which the microsomal protein had been coagulated by heating to 80 C for 3 min, were performed. UDCA induced a large number of exchanges in conjunction with all S9 mixes, and while small differences attributable to treatment exist, the activity of NADPH-requiring mixed function oxidases is not necessary. The heat-treated S9 mix increased the toxicity and the frequency of exchanges relative to control. (31 Refs)

49. METABOLISM, DISTRIBUTION, AND EXCRETION OF THE FLAME RETARDANT, TRIS(2,3-DIBROMOPROPYL) PHOSPHATE (TRIS-BP) IN THE RAT: IDENTIFICATION OF MUTAGENIC AND NEPHROTOXIC METABOLITES.

Lynn RK, Garvie-Gould C, Wong K, Kennish JM
Dept. Pharmacology, Oregon Health Sciences Univ., Portland, OR 97201
Toxicol Appl Pharmacol; 63(1):105-119 1982

Metabolism and distribution of tris(2,3-dibromopropyl) phosphate (Tris-BP) were followed in male Sprague-Dawley rats for 5 days after iv injection of 14C-Tris-BP. Approx 58% of radiolabel was excreted within 24 hr, and 86% by 5 days. At this time approx 9% of the dose remained in the body (95% recovery). Studies in several animals with exteriorized bile ducts showed that approx 34% of the dose was excreted in the bile at 24 hr, but that a minimum of 74% of this was reabsorbed. High pressure liquid chromatography demonstrated numerous radiolabeled components, of which bis(2,3-dibromopropyl) phosphate (Bis-BP) and 2,3-dibromopropanol (DBP) were identified. Tris-BP disappeared rapidly in tissues and was undetectable at 8 hr, but the half-life of Bis-BP was relatively long. Bis-BP concentrated in lung, muscle, fat, and especially blood, where it accounted for approx 90% of the radiolabel at 30 min and 8 hr. At 5 days the concentration of radiolabel was highest in the kidneys, 11x the av whole body concentration. This may be related to the polyuria induced by large doses of Tris-BP. In Ames mutagenicity testing on TA100 and TA1535, with microsomal activation, Tris-BP was most mutagenic, with Bis-BP and DBP approx equal at all concentrations except the highest (1,000 nanomole/plate), where Bis-BP was approx 80% more active. Previous work on Tris-BP is discussed and compared with these findings. (21 Refs)

50. MUTAGENICITY SCREENING OF CRUDE DRUGS WITH BACILLUS SUBTILIS REC-ASSAY AND SALMONELLA/MICROSOME REVERSION ASSAY.

Morimoto I, Watanabe F, Osawa T, Okitsu T, Kada T
Saitama Inst. Public Health, Kamiokubo 639-1, Urawa-shi, Saitama-ken 338, Japan
Mutat Res; 97(2):81-102 1982

The mutagenicity of 104 commercial crude drugs (plant extract) was studied using the Bacillus subtilis rec-assay and the Salmonella/microsome reversion assay (Ames strains TA98 and TA100). The rec-assay disclosed mutagenic activity for 13/104 water extracts and 27/104 methanol extracts. The Ames assays (with or without metabolic activation) disclosed mutagenic activity for 24/104 water extracts and 16/104 methanol extracts. In all, 45/104 crude drugs showed mutagenic activity. (14 Refs)

51. A REVIEW OF THE GENOTOXICITY OF FOOD, DRUG AND COSMETIC COLOURS AND OTHER AZO, TRIPHENYLMETHANE AND XANTHENE DYES.

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Mutat Res, 98(2):101-248 1982

Genetic hazards associated with the production and use of synthetic and natural dyes used as food additives are reviewed. Genotoxicity of structurally-related azo, triphenylmethane and xanthene dyestuffs used in drugs and cosmetics was considered. Particular attention was given aminoazobenzene and several of its derivatives with respect to carcinogenicity and mutagenicity. Activities of these dyes in short-term tests for genotoxicity are stressed; animal carcinogenicity and nonspecific toxicity is not emphasized. Dye metabolism and activities of dye metabolites are reviewed. Structural features of these dyes and their metabolites were assessed and an attempt was made to evaluate data with respect to correlations with tumor-inducing ability and to levels of environmental exposure. More than half of the dyes discussed have shown activity in at least one short-term test. Certain food colors may be active in vitro at levels comparable to those ingested daily. Natural colors, except for curcumin and riboflavin, were inactive. More data are required for all of the various dye groups, particularly for synthetic and natural non-azo compounds. Discussion of structure-activity must be tentative because of the lack of data and problems due to active sample contaminants. The presence of various substituents may be potentiating. No currently permitted food color which is inactive in short-term tests is considered a carcinogen, although some active colors require further animal testing. A human cancer hazard may exist where significant amounts of finished benzidine dye samples are handled. Such risks from exposures to other colors and the possibility of human germ-line mutation induction by dyes cannot be assessed in a meaningful manner. (365 Refs)

52. INDUCTION OF SISTER-CHROMATID EXCHANGES, CELL-CYCLE DELAY AND CHROMOSOMAL ABERRATIONS BY HUMAN URINE CONCENTRATES.

Beek B, Aranda I, Thomson E
Institut fur Genetik, Freie Universitat Berlin, Arnimalee 5-7, 1000 Berlin 33, W. Germany
Mutat Res; 92(1/2):333-360 1982

Human urine concentrates (HUC) prepared using XAD-2 resin induced sister chromatid exchanges, chromosomal damage, and cell cycle delays in cultured Chinese hamster ovary cells, without the use of metabolic activation. The mutagenic activities of HUC from smokers, nonsmokers, and patients with alcoholic cirrhosis of the liver were about the same. Experiments with variant HUC preparative procedures showed that rapid saturation of the resin by nonpolar compounds from human urine may result in underestimation of the amount of mutagenic substances in a given HUC sample. (26 Refs)

53. CAN WE DETERMINE MUTAGENICITY OR ONLY A MUTAGENIC POTENTIAL?

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Mutat Res; 92(1/2):3-7 1982

When an agent is identified as a 'mutagen', the assay results have identified only the agent's mutagenic potential, whose expression in a given biosphere can be masked by detoxification mechanisms and/or altered by metabolic activation. Certain types of mutagens may at present be overlooked because most assays of environmental mutagenicity ignore chromosomal malsegregation. The assessment of the mutagenic potential of a given agent in man requires the evaluation of all potential sources of its metabolic activation. It is almost impossible to detect and test all potentially mutagenic metabolites of a given agent. (15 Refs)

54. ON THE PROBLEM OF MICROBIAL MUTAGENESIS.

Gericke D
Abt. fur Offentlichkeitsarbeit, Hoeschst AG, Wiss. Buro, Postfach 800320, 6230 Frankfurt/M. 80, W. Germany
Onkologie; 5(1):30-32,34-35 1982

Mutagenicity tests using microorganisms are the Salmonella-typhimurium test (Ames), the test with a polymerase A deficient Escherichia coli, the Saccharomyces cerevisiae D3 system and the Neurospora crassa test. Differences in results of Ames-test may be due to differences preserving the tester strains, the choice of solvent and the dosage of the test compounds, last not least is the production of S-9. The polymerase A deficient Escherichia coli system seems easier to handle than the Saccharomyces cerevisiae or Neurospora crassa-test. The metabolic activation with different forms of S-9 is needed in the Salmonella- and the Escherichia coli-system. Nevertheless it is not possible to decide if a substance is carcinogenic for human beings or animals with microbial mutagenicity tests only. (Author abstract) (20 Refs) (In GER)

55. SUSPECTED CANCER-CAUSING AGENTS IN THE HOSPITAL ENVIRONMENT.

Kubinski H, Kubinski ZO, David M
4605 Medical Science Center, 1300 University Ave., Madison, WI, 53706
Ecotoxicol Environ Saf; 6(1):9-18 1982

Various substances in patient hospital rooms were tested for carcinogenicity in a short-term, in vitro DNA cell-binding (DCB) test. Substances tested included 24 cleaning agents, 7 cosmetics, 4 glues and other home repair articles, 4 insecticides and insect repellents, 4 first aid articles and local skin disinfectants, and 8 miscellaneous articles. Seventeen of the substances appeared able to induce neoplasia. Neoplastic potential was suggested for an upholstery cleaner, a toilet bowl cleaner, an all-purpose cleaner, and a cleaning agent with fungicidal properties; and for a spray deodorant, an antidandruff shampoo, a disinfectant skin cleanser, two mosquito repellents, two disinfectant sprays from first aid items, two parts of epoxy glue, and two shoe polishes. Metabolic activation was required by 9/17 positive substances. Articles such as cleaning agents, purchased in large quantities by hospitals, should be screened for potential carcinogenicity by a short-term assay performed in the laboratory of the hospital. Alternatively, proof of testing by the manufacturer should be mandatory. (20 Refs)

56. THE USE OF LARVAL STAGES OF DROSOPHILA IN SCREENING FOR SOME NATURALLY OCCURRING MUTAGENS.

Clark AM
Sch. Biological Sciences, Flinders Univ. South Australia, Bedford Park, 5042, Australia
Mutat Res; 92(1/2):89-97 1982

The mutagenic effects of several naturally occurring substances were tested in X-linked recessive lethal assays in larval and adult male Drosophila. The substances tested were heliotrine, rutin, quercetin (rutin aglycone), juglone (5-hydroxy 1,4-naphthoquinone), bracken fern extract, and fresh or dried leaves of Russian comfrey (Symphyton officinale). Extracts of fresh comfrey leaves were mutagenic in the Drosophila test, but the dried leaves were not. The results suggested that comfrey tea (widely promoted in health food stores) is unlikely to pose a mutagenic hazard to humans, although this may not be the case for fresh comfrey leaves used in salads. In general, the larval stages (notably the third-instar stage) were more susceptible to the mutagenic effects of these substances than the adult males. If this higher sensitivity is based on metabolic activation by the fat body, this would imply the passage of metabolites from fat body cells to the larval testis. Further tests with a wider range of mutagens are required to evaluate the tentative conclusion that Drosophila larvae are often more sensitive than adults for screening purposes. Both larval and adult stages should be tested before it is concluded that a suspected mutagen is inactive in the Drosophila sex-linked recessive lethal test. (28 Refs)

57. MUTAGENICITY OF AIRBORNE PARTICLES IN RELATION TO TRAFFIC AND AIR POLLUTION PARAMETERS.

Moller M, Alfheim I, Larssen S, Mikalsen A
Central Inst. for Industrial Res., P.O. Box 350, Blindern, Oslo 3, Norway
Environ Sci Technol; 16(4):221-225 1982

Air samples were taken day and night in a park and at 2 and 25 m heights in a nearby heavy traffic street. Extracts were tested for mutagenicity with and without S9 metabolic activation on Salmonella typhimurium TA98. S9 increased mutagenicity 2-3x in the 2 m street day samples. Day samples, park or street 25 m, were not influenced by S9, and had only 5-25% of the activity of day 2 m street samples. Depression of 2 m street activity at night corresponded to decrease in traffic. (26 Refs)

BINDING OF CARCINOGENS AND THEIR METABOLITES TO MACROMOLECULES

58. CARCINOGENIC EPOXIDES OF BENZO[A]PYRENE AND CYCLOPENTA[CD]PYRENE INDUCE BASE SUBSTITUTIONS VIA SPECIFIC TRANSVERSIONS.

Eisenstadt E, Warren AJ, Porter J, Atkins D, Miller JH
Dept. Microbiology, Harvard Sch. Public Health, Boston, MA, 02115
Proc Natl Acad Sci USA; 79(6,part1):1945-1949 1982

We have determined the spectrum of base-pair substitution mutations induced in the lacI gene of uvB- strain of Escherichia coli by two polycyclic aromatic hydrocarbons (+-)7alpha,8beta-dihydroxy-9beta,10beta-epoxy-7,8,9,10 tetrahydrobenzo[a]pyrene (BPDE), and 3,4-epoxycyclopenta[cd]pyrene (CPPE). Approximately 10% of all lacI mutations induced by either BPDE or CPPE are nonsense mutations, suggesting that base-pair substitutions are a large fraction of the mutational events induced by these agents in the uvB- bacteria. Both carcinogens specifically induced the G-C to T-A and, to a lesser extent, the A-T to T-A transversions. One possible mechanism for transversion induction at G-C sites by BPDE might involve carcinogen binding to the exocyclic amino group of guanine in the template strand followed by a rotation of the modified base around its glycosylic bond from the anti to the syn conformation. This could allow specific pairing of modified bases with an imino tautomer of adenine. (Author abstract) (26 Refs)

59. BENZPYRENE GROUPS BIND PREFERENTIALLY TO THE DNA OF ACTIVE CHROMATIN IN HUMAN LUNG CELLS.

Arrand JE, Murray AM
Dept. Biochemistry, St. Mary's Hosp. Medical Sch., London W2 1PG, England
Nucleic Acids Res; 10(5):1547-1555 1982

The cells of the bronchial epithelium of man are targets for benzo(a)pyrene carcinogenesis. when cultures of these cells, and of non-target fibroblasts, are exposed to [3H]benzo(a)pyrene, we find that the epithelial cells metabolize and bind to DNA far greater amounts of benzpyrene than do fibroblasts. By analysis of nuclei of benzypyrene treated cells for sensitivity to limited digestion with pancreatic DNase I, we have shown that benzpyrene groups bind initially to the DNA of expressed (DNase I sensitive) regions of chromatin in both cell types. Covalent binding of benzpyrene groups to nonexpressed (DNase I resistant) regions follows rapidly in the target epithelial cells. These maintain high levels of carcinogen adducts in their DNA. In fibroblasts, benzyprene group binding to non-expressed DNA occurs more slowly and active removal of adducts from the DNA is evident. (Author abstract) (21 Refs)

60. ELECTRICALLY INDUCED FLUORESCENCE AS A METHOD FOR STUDYING BENZA[A]PYRENE BINDING TO DNA.

Ridler PJ, Jennings BR
Electro-Optic Group, Physics Dept., Brunel Univ., Uxbridge, Middlesex UB8 3PH, England
FEBS Lett; 139(1):101-104 1982

A new physical method developed for studying the binding geometry of fluorescent groups to macromolecules was applied in the study of trans-7,8-dihydroxy-anti-9,10 epoxy-7,8,9,10-tetrahydrobenzo[a]pyrene derivatives (BPDF), naive benzo[a]pyrene (BP), and proflavine, when independently bound to DNA. The method is sensitive to the presence of small amounts of bound dye molecules on nucleic acid. Results indicate that the pyrene fluorophore of BPDE does not intercalate the DNA helix, at least in the way that proflavine or BP do. The method appears to be an effective indicator of binding geometry for polycyclic hydrocarbons on nucleic acids. (18 Refs)

61. SIMILAR LEVEL OF METABOLIC ACTIVATION OF BENZO(A)PYRENE IN PERFUSED RAT LUNG AND LIVER AND PROTECTION OF LUNG BY LIVER IN A COMBINED PERFUSION SYSTEM.

Klaus E, Foth H, Kahl R, Kahl G
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Biochem Biophys Res Commun; 105(2):596-602 1982

The binding of benzo(a)pyrene metabolites to DNA, RNA, and protein in perfused rat liver and lung in situ and the influence of the liver on the level of nucleic acid and protein modification by benzo(a)pyrene in the lung were investigated. In the liver of 5,6-benzoflavone pretreated rats, irreversible binding of metabolically activated benzo(a)pyrene to both nucleic acids and protein reaches a peak at 15 min and then declines. In contrast, binding in the lung continuously increases over the 2 hr perfusion period. The extent of binding is of the same order of magnitude in the liver and lung of cytochrome P-448-induced (ie 5,6-benzoflavone-induced) animals. At 15 min, binding to both DNA and RNA in the liver exceeds binding to nucleic acids of the lung by a factor of 3-6; this relations is nearly reversed after 2 hr of perfusion. Protein binding is more pronounced in the lung than in the liver over the entire 2 hr perfusion. The longer persistance of benzo(a)pyrene binding in the lung may contribute to the fact that the lung and not the liver is the target organ of benzo(a)pyrene carcinogenesis. Following the insertion of a liver into the perfusion circuit of the lung, the total irreversible binding of metabolically activated benzo(a)pyrene to DNA, RNA, and protein is reduced, this effect being more pronounced in 5,6-benzoflavone-induced animals. Thus the high detoxication capacity of the liver can protect other organs having lower xenobiotic metabolizing activity against benzo(a)pyrene. (16 Refs)

62. METABOLISM AND DNA BINDING OF BENZO[A]PYRENE IN CULTURED HUMAN BLADDER AND BRONCHUS.

Stoner GD, Daniel FB, Schenck KM, Schut HA, Goldblatt PJ, Sandwisch DW
Dept. Pathology, Medical Coll. Ohio, 3000 Arlington Ave., Toledo, OH, 43614
Carcinogenesis; 3(2):195-201 1982

The metabolism of benzo[a]pyrene (BP) was examined in explant cultures of human bladder and bronchus. Three-day cultures were exposed to radiolabeled BP for 24 hr, and the metabolism was determined by analysis of the level of binding of reactive metabolites to DNA, and by the release of metabolites into the medium. For a given individual, the DNA binding level and extent of metabolism was usually higher in the bladder than in the bronchus. In specimens obtained from 16 individuals, the average DNA-binding levels for BP-DNA adducts following a 24 hr exposure to 1 uM BP were 6.4 +-5.0 umol BP/mol deoxyribonucleotide for the bladder and 3.1 +-1.9 umol BP/mol deoxyribonucleotide for the bronchus. The major BP - DNA adduct in both tissues co-chromatographed with one of the adducts formed by reaction of r-7,t-8-dihydroxy-t-9,10-oxy-7,8,9,10 tetrahydrobenzo[a]pyrene with deoxyguanosine using high-pressure liquid chromatography. In tissues obtained from the same individual, the binding levels of BP metabolites to bladder cell DNA was not strongly correlated to that of bronchial cell DNA (r = 0.54). The medium of both tissues contained small amounts of free, unconjugated metabolites of BP (less than 3% of the total) and large amounts (30-85% of the total) of unidentified, highly polar material. Human bladder appears to be the most active human explant tissue yet studied with respect to its ability to activate BP to DNA binding forms. The relevance of this observation to human bladder cancer is, as yet, unknown. (Author abstract) (40 Refs)

63. THE EFFECT OF BENZO[A]PYRENE ON SPONGES AS MODEL ORGANISMS IN MARINE POLLUTION.

Zahn RK, Kurelec B, Zahn-Daimler G, Muller WE, Rijavec M, Batel R, Given R, Pondeljak V, Beyer R
Physiologisch-Chemisches Institut, Johannes-Gutenberg-Universitat, Duesbergweg, D-6500 Mainz, W. Germany
Chem Biol Interact; 39(2):205-220 1982

The majority of the investigations were performed with the marine sponge Tethya lyncurium at concentrations of 2 x 10(-8) to 1 x 10(-11) g/ml of benzo[a]pyrene (BaP). Sea-pollution was characterized as BaP equivalent activity in the Ames test. Increased activity of ornithine decarboxylase (ODC) was observed when sponges were artificially exposed at polluted marine areas for 3 wk. In contrast, to the situation in higher animals no ODC induction of the fast type was observed. Mixed function oxygenases (MFO) were not detected in sponges no could they be induced as in vertebrates. BaP was absorbed by Tethya and concentrated 30-60 fold. In live, but not dead, artificially perfused sponged [3H]- and [14C]BaP-radiolabel became firmly associated with DNA, RNA and protein of the sponges. The association persisted in isolated fractions, in nucleotides, in nucleosides and in protein hydrolysates. The BaP binding ratio to DNA was found to be strongly correlated to the concentration of BaP. Light modifiers BaP and thus enables binding. In the dark only very low association, if any, is observed. The possible consequences of these findings are discussed. (Author abstract) (48 Refs)

64. THE EFFECTS OF METHYLATED THYMIDINES UPON CULTURES OF V79 CELLS AND THE MECHANISM OF INCORPORATION OF O(4)-METHYLTHYMIDINE INTO THEIR DNA.

Brennand J, Saffhill R, Fox M
Paterson Lab., Christie Hosp. and Holt Radium Inst., Manchester M20 9BX, England
Carcinogenesis; 3(2):219-222 1982

High concentrations of O2-methylthymidine, 3-methylthymidine and O4-methylthymidine (O4-MedT) have little effect on the colony forming ability of cultured Chinese hamster (V79) cells. However, the methylated derivatives enhance the toxic effects of thymidine (dT) at concentrations at which the modified nucleosides alone show no toxicity. O4-MedT was the only modified nucleoside which is incorporated into V79 cell DNA at a detectable level. In the presence of added dT there is an increase in the amount of O4-MedT incorporated. O4-MedT did not induce mutation, either forward or reverse, in V79 cells. The results indicate that O4-MedT is incorporated into DNA as an analogue of deoxycytidine and once incorporated behaves as cytidine during DNA synthesis, in contrast to O4-MedT produced in cellular DNA by methylating carcinogens which is miscoding and potentially mutagenic. (Author abstract) (19 Refs)

65. SOMATIC MUTATION AND NEOPLASTIC TRANSFORMATION INDUCED BY [METHYL-(3)]THYMIDINE.

Lin SL, Takii M, Ts'o PO
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Radiat Res; 90(1):142-154 1982

Effects of tritiated thymidine (3H-TdR) on neoplastic transformation and somatic mutation in Golden Syrian hamster embryo (GSHE) fibroblast cultures were studied and compared with those in cultures treated with tritiated uridine (3H-UdR). Normal GSHE cells were exposed to 3H-TdR for 17 hr, then grown briefly in deoxycytidine- and thymidine-containing medium. A multihit mechanism for reduction of colony formation was suggested, with a Dq value of 0.01 uCi/ml and a D0 value of 0.04 uCi/millimole. Mutagenicity of 3H-TdR was examined with a tumor line, BP6T, established from benzo(a)pyrene-treated GSHE cultures. Mutagenicity was studied at loci coding for hypoxanthine phosphoribosyltransferase (HPRT) and for the Na+/K+ ATPase. A linear dose-response curve was obtained for mutation at the HPRT locus. 3H-TdR incorporation over the concentration range of 0-0.04 uCi/ml corresponded to a biologically effective dose of 0-271 rad. An effective dose of 0.10 rad/decay and a total dose of 2,831 decays were calculated. Over the same tritium dose range, 5-3H-UdR did not induce HPRT- mutations. No mutations to ouabain resistance were observed in any experiments. All cultures treated with 0.04 uCi/ml 3H-TdR became tumorigenic, while control cultures did not. Neoplastic transformation began with morphological alteration, followed by enhanced fibrinolytic activity and the ability to clone in medium containing 1% serum or soft agar. DNA damage caused by 3H-TdR was manifested by induction of somatic mutation, most likely of a frameshift/deletion nature. The findings support the conclusion that DNA damage alone is sufficient to initiate neoplastic transformation. (32 Refs)

66. HEPATIC MICROSOMAL METABOLISM AND MACROMOLECULAR BINDING OF THE ANTIOXIDANT, N-PHENYL-2-NAPHTHYLAMINE.

Anderson MM, Mitchum RK, Beland FA
(c/o Beland) Natl. Center Toxicological Res., Food and Drug Admin., Jefferson, AR, 72079
Xenobiotica, 12(1):31-43 1982

The hepatic microsomal metabolism of N-phenyl-2-naphthylamine (P2NA), an industrial antioxidant and suspected carcinogen, was studied in seven mammalian species to determine if N-dephenylation, reported to occur in vivo, could be demonstrated in vitro and if macromolecular binding occurs without an obligatory N-dephenylation. The rate of hepatic microsomal metabolism decreased in the order: hamster very much greater than mouse, greater than rat, approx equal to monkey, approx equal to dog, greater than human, approx equal to pig. Metabolism was increased by pretreatment with 3-methylcholanthrene or phenobarbital and decreased by carbon monoxide or 2-[(2,4-dichloro-6-phenyl)phenoxy] ethylamine, which indicated the involvement of cytochrome P-450 rather than the flavoprotein mixed-function oxidase. All seven species produced two major metabolites identified as 6-hydroxy-P2NA and 4'-hydroxy-P2NA. The carcinogen 2-naphthylamine was not detected in the microsomal incubations. Incubations in the presence of 18O2 indicated that the oxygen incorporated in the products came from molecular oxygen. There was a time-dependent linear increase in covalent binding of P2NA to microsomal protein and the extent of binding approx paralleled the rate of metabolism. Thus, macromolecular binding of this aromatic amine appears to occur without an obligatory N dephenylation and may be due to the metabolic formation of epoxides. (Author abstract) (31 Refs)

67. DNA PRECURSOR POOL: A SIGNIFICANT TARGET FOR N-METHYL-N-NITROSOUREA IN C3H/10T1/2 CLONE 8 CELLS.

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Dept. Pathology, Cancer Res. Center, Univ. North Carolina Medical Sch., Chapel Hill, NC, 27514
Proc Natl Acad Sci USA; 79(7):2211-2215 1982

Synchronized C3H/10T1/2 clone 8 cells were treated in vitro with a nontoxic dose of N-methyl-N-nitrosourea during their S phase. Chromatographic isolation of the deoxyribonucleotide DNA precursor pool and measurement of the precursor content per cell showed that a nucleic acid residue in the precursor pool is 190-13,000 times more susceptible to methylation than a residue in the DNA duplex, depending on the site of methylation. This conclusion comes from measurements indicating that, for example, the N-1 position of adenine in dATP is 6.3 times more methylated than the same position in the DNA, even though the adenine content of the pool is only a fraction (0.0005) of the adenine content of the DNA helix. The comparative susceptibility between pool and DNA was found to vary with the site of methylation in the order the N-1 position of adenine greater than phosphate greater than the N-3 position of adenine greater than the O6 position of guanine greater than the N-7 position of guanine. The significance of these results for chemical mutagenesis and carcinogenesis is discussed. (Author abstract) (25 Refs)

68. DIMETHYLNITROSAMINE ADDUCTS EXCRETED IN RAT URINE.

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Chem Biol Interact; 39(2):139-148 1982

Rats were injected with [14C]dimethylnitrosamine and urine was collected up to 5 days after the injection. Urine samples were concentrated and subjected to Sephadex G-10 chromatography. Three peaks of radioactivity (I-III, in the order of elution) were observed for all injection times. The peaks were analyzed further by cation exchange and thin-layer chromatography and by phase-separation (pH-determination). The pK-determinations and the chromatographic properties suggested that Sephadex fraction I is composed of methylated amino acids, such as N-acetyl-S-methylcysteine, 1-methylhistamine and S-methylcysteine, in addition to radioactive methionine. Sephadex fraction II was composed of allantoin and of a metabolite of thiazolidine-4-carboxylic acid. The latter compound was a reaction product of formaldehyde and cysteine, indicating activity of the formaldehyde moiety released from dimethylnitrosamine. By gel filtration properties Sephadex fraction III indicated identity as 7-methylguanine. Altogether the urinary radioactivity accounted for about 9% of the applied dose. (Author abstract) (27 Refs)

69. POLY(ADP-RIBOSYLATION) IN N,N-DIETHYLNITROSAMINE-TREATED MICE.

Shugart L, Chastain B, Holland JM
Biology Div., Oak Ridge Natl. Lab., Oak Ridge, TN, 37830
Int J Biochem; 14(3):231-233 1982

C3H mice were treated with single injections of N,N-diethylnitrosamine (DEN: 35-100 mg/kg body wt, ip). Liver nuclei of the treated animals were examined for poly(ADP-ribose) and the conjugate enzyme poly(ADP-ribose) polymerase. The poly(ADP-ribose) content increased with time, showing a peak at about 4 hr post-injection and subsequently falling to pre-injection levels. This effect was dose dependent and was not observed in a control experiment which examined the nuclei of the kidney, a non-target tissue of DEN. The level of poly(ADP-ribose) polymerase also exhibited a transitory increase which was dose dependent. The return of poly(ADP-ribose) levels to the pre-injection level is probably not due to the accompanying loss of polymerase activity but instead to the transient induction of poly(ADP-ribose) glycohydrolase. DEN and other N-nitroso compounds are thought to exert their carcinogenicity via alkylation of DNA. Thus, the measurement of poly(ADP-ribose) and/or its polymerase may provide a basis for measuring DNA damage resulting from carcinogen exposure. (23 Refs)

70. IN VIVO BINDING OF N-NITROSOPYRROLIDINE AND N-NITROSOHEXAMETHYLENEIMINE TO NON-PURINE SITES ON RAT LIVER DNA.

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Eppley Inst. for Res. in Cancer, Univ. Nebraska Medical Center, Omaha, NE, 68105
Cancer Lett; 15(3):329-334 1982

Treatment of male MRC-Wistar rats with labeled N-nitrosopyrrolidine (NPYR) and N-nitrosohexamethyleneimine (NHX) is reported. Radioactivity profiles of the 70% perchloric acid hydrolysates of liver DNA and RNA from [3H]NHX-treated rats after cation exchange are presented. The main peak is in the same numbered fraction for both DNA and RNA, and is apparently volatile, since 90% was lost on evaporation to dryness in current nitrogen. Chromatography of DNA and RNA hydrolysates on Sephadex G-10 produced similar radioactive profiles and resulted in a single major peak of volatile substance in corresponding fractions. The results contrast with the radioactive components (RC) separated by cation exchange chromatography of 1 M HCl hydrolysates of the nucleic acids from NHX-treated rats. RNA yielded five main RC. DNA had only four RC, with 5% of the radioactivity in a peak at the same elution vol as 1,6-hexanediol. The chromatogram of the DNA mild acid hydrolysate from NPYR-treated rats had an identical feature. These results suggest that either the two nitrosamines do not interact with purines or, if purine interaction takes place, the groups attached to the purine alter their chromatographic properties to such an extent that they elute from a Sephadex G-10 column with apurinic acid. Experiments were performed to test this hypothesis and the results obtained suggest that radioactivity was still attached to the large-mol-wt apurinic acid remaining in the dialysis tubing. The data could be due to alkylation that took place only at the phosphate groups or to a metabolite produced from NHA with two active sites, capable of forming cross-links. The findings suggest that extensive phosphotriester formation and/or cross-link formation might be a feature common to DNA alkylated by alicyclic nitrosamines. (9 Refs)

71. MUTAGENICITY AND DNA-MODIFYING ACTIVITY OF 2-NITROPROPANE.

Speck WT, Meyer LW, Zeiger E, Rosenkranz HS
Dept. Pediatrics, Case Western Reserve Univ., Cleveland, OH, 44106
Mutat Res; 104(1-3):49-54 1982

DNA-modifying activity and mutagenicity of the industrial solvent 2-nitropropane and also 1-nitropropane, 1-aminopropane, and 2-aminopropane were examined. Using the Salmonella typhimurium mutagenicity assay, 2-nitropropane was shown to be mutagenic, 1-nitropropane had marginal activity, and 1- and 2-aminopropane were not mutagenic. Only 2-nitropropane showed DNA-modifying activity. The mutagenic, and presumably carcinogenic, effects of 2-nitropropane may be due in part to a direct, non-enzymic, reaction between the chemical and intracellular DNA. (10 Refs)

72. NONDETECTION OF O(6)-METHYLGUANINE IN RAT DNA FOLLOWING IN VIVO TREATMENT WITH LARGE DOSES OF CIMETIDINE ALONE OR IN COMBINATION WITH SODIUM NITRITE.

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Cancer Res; 42(5):1962-1966 1982

Cimetidine was administered by stomach tube to rats at 70 or 700 mg/kg, doses corresponding to 5 or 50 times, respectively, the typical daily dose of individuals on cimetidine treatment. In some cases, cimetidine (70 mg/kg) was administered in combination with a two-fold molar excess of sodium nitrite. This treatment was carried out up to six times over a 3-day period, the pH of the rat stomach being maintained at 2.2 to 3.0 for about 1 hr after each treatment. The DNA of the stomach, liver, and intestines (large and small pooled together) were isolated 6 hr after cessation of treatment and analyzed for the presence of O6-methylguanine using a sensitive and specific radioimmunoassay. No evidence could be obtained for the presence of this methylated base in any of the DNA samples examined, the limit of detection being 3 μmol O6-methylguanine per mol guanine. We suggest that the observed lack of DNA methylation may be primarily due to the slow rate of nitrosation of cimetidine in combination with its rapid absorption into the blood stream. (Author abstract) (38 Refs)

73. CYTOSOLIC AND NUCLEAR BINDING OF 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN TO THE AH RECEPTOR IN EXTRA-HEPATIC TISSUES OF RATS AND MICE.

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Eur J Biochem; 123(1):209-215 1982

Induction of aryl hydrocarbon hydroxylase (cytochrome P1-450) is mediated by the Ah receptor which initially binds inducing chemicals in the cytoplasm, after which the inducer-receptor complex translocates into the nucleus. Ah receptor can be detected and quantified by sucrose-density-gradient analysis of its binding to 2,3,7,8-tetrachloro[3H]dibenzo-p-dioxin. Labeling in vitro of cytosols from C57BL/6J mice and Sprague-Dawley rats reveals Ah receptor in several tissues, with concentrations in the rank order for C57BL/6J mice: liver greater than lung much greater than kidney approx = thymus approx = small intestine greater than prostate; for Sprague-Dawley rats: liver approx = lung approx = thymus much greater than small intestine much greater than greater than kidney. Cytosol receptor was not detectable by assays in vitro on skin, skeletal muscle, heart, brain or testis of C57BL/6J mice or Sprague-Dawley rats, nor was specific receptor detectable in cytosol from any tissue of genetically 'non-responsive' DBA/2J mice. Injection in vivo of 2,3,7,8-tetrachloro[3H]dibenzo-p-dioxin led to recovery of specific nuclear Ah receptor from liver, lung and kidney of both genetically 'responsive' C57BL/6J mice and 'non-responsive' DBA/2J mice as well as Sprague-Dawley rats. Nuclear Ah receptor concentrations were lower in DBA/2J mice than in C57BL/6J mice receiving the same dose, and nuclear receptor was detectable only with injection of high doses of 2,3,7,8-tetrachloro[3H]dibenzo-p-dioxin. Although cytosolic Ah receptor in DBA/2J mice appears to be 'defective' and cannot be detected directly by assays in vitro, recovery of specific receptor from nuclei of DBA/2J tissues implies that binding of 2,3,7,8-tetrachloro[3H]dibenzo-p-dioxin to Ah receptor does occur in vivo in these animals; this may explain the ability of 'non-responsive' DBA/2J mice to exhibit induction of aryl hydrocarbon hydroxylase when treated with the very potent inducer, 2,3,7,8-tetrachlorodibenzo-p-dioxin. (Author abstract) (12 Refs)

74. INFLUENCE OF EXPERIMENTAL CONDITIONS AND DNA REPAIR ABILITY ON EMS-INDUCED MUTAGENESIS AND DNA BINDING IN ESCHERICHIA COLI K12: COMPARISON WITH MAMMALIAN CELL MUTAGENESIS.

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Dept. Radiation Genetics and Chemical Mutagenesis, State Univ. Leiden, Leiden, The Netherlands
Mutat Res; 92(1/2):15-27 1982

The magnitude of ethyl methanesulfonate (EMS)-induced DNA binding and mutagenesis under different conditions was studied in Escherichia coli K12/343/113, several mutant sublines of this strain, and mammalian cell lines V79 and L5178Y. Under the same exposure conditions (120 min at 37 C, pH 7.2) and at different EMS concentrations (2.5-50 mM), the bacteria and mammalian cells showed similar levels of DNA alkylation (1.7 x 10(-4) -1.5 x 10(-3) ethylations/nucleotide). In stationary E coli cultures, the presence of L-arginine, D-glucose, and fetal calf serum during EMS exposure markedly enhanced the yields of EMS-induced mutations but did not affect the level of DNA alkylation. Nutrient accumulation by the cells may have enhanced their capacities for genetic fixation and/or phenotypic expression of premutational DNA changes. Because the mammalian cells were significantly more sensitive than repair-proficient E coli to the lethality of a given EMS concentration, the mammalian cells may have a larger genetic and/or physiologic target for cytotoxicity or a lesser ability to repair EMS-induced DNA damage. In bacterial mutants NALr and VALr, and in thioguanine-resistant (hypoxanthine-guanine phosphoribosyltransferase-deficient) and 5-bromo-2'-deoxyuridine-resistant (thymidine kinase-deficient) mammalian cells, low EMS concentrations (up to 7 mM) led to a linear dose-effect (mutation frequency) relationship with no evidence of a threshold. These experiments did not determine whether the very similar dose-effect relationships in E coli and the mammalian cells indicated that the same EMS-induced DNA adducts were responsible for the observed genetic effects. (20 Refs)

ALTERATION OF MIXED FUNCTION OXIDASES BY CARCINOGENS

75. RELATION BETWEEN THE SOMATIC TOXICITY OF DIMETHYLNITROSAMINE AND A GENETICALLY DETERMINED VARIATION IN THE LEVEL AND INDUCTION OF CYTOCHROME P450 IN DROSOPHILA MELANOGASTER.

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Mutat Res; 92(1/2):161-168 1982

Enzyme induction and metabolism in Drosophila were studied with the use of somatic toxicity of dimethylnitrosamine (DMN). The activity of cytochrome P450 (P450) in insecticide-resistant Drosophila melanogaster (Hikone R and 5H5 strains) was higher than the P450 activity of insecticide-sensitive strains. Phenobarbital (PB) induced P450 in the sensitive strains but not in the resistant strains. The toxicity and mutagenicity of DMN and the uptake of vinyl chloride (VC) were higher in the resistant strains than in the sensitive strains. The correlation between DMN toxicity and the metabolic differences between the insecticide-resistant and sensitive strains was demonstrated by the increased toxicity of DMN after PB pretreatment in the sensitive strains but not in the resistant strains. A dominant gene, responsible for the patterns of VC and presumably DMN metabolism and the non-inducibility of P450 in the Hikone R strain, was located in region 66 cM of chromosome 2, near the vg gene. This gene may be the major gene responsible for the insecticide resistance of the strain. Genetic variation in the mixed function oxidase system associated with insecticide resistance in Hikone R does not apply to the enzyme system as a whole. Benzo(a)pyrene monooxygenase activity and inducibility are the same in the insecticide-sensitive and Hikone R strains of Drosophila. (12 Refs)

76. EFFECT OF MICROSOMAL CYTOCHROME P-450 ISOENZYME INDUCTION ON THE MUTAGENIC ACTIVATION OF 2-AMINOANTHRACENE.

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Cancer Res; 42(5):1722-1726 1982

Two rabbit microsomal cytochrome P-450 isozymes, Forms 4 and 6, which are differentially induced by 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) in the liver in an age-dependent fashion, catalyze the activation of 2-aminoanthracene to a mutagen in the Ames Salmonella mutagenesis assay. We have shown previously that in the presence of saturating concentrations of 2-aminoanthracene, Form 4 is 15-fold more active than Form 6 in the activation of this mutagen. Similar differences in the activation of 2-aminoanthracene are observed between liver microsomes isolated from TCDD-treated adult rabbits, in which Form 4 predominates, and microsomes from rabbit neonates exposed transplacentally to TCDD prior to birth, in which Form 6 predominates. However, when the extent of mutagenesis is limited by the amount of 2-aminoanthracene and is independent of the rate of activation, the number of revertants produced is similar for microsomes isolated from either newborn or adult TCDD-treated rabbits. Under these conditions, the extent of mutagenesis obtained for a given amount of 2-aminoanthracene will depend on the balance between activation and competing reaction pathways leading to detoxication. Thus, differences in the rate of activation between adult and newborn microsomes are probably offset by similar differences in the rates of competing pathways of metabolism. This is consistent with the finding that the overall rate of 2-aminoanthracene metabolism by the adult microsomes is greater than that of the neonate. In order for the extent of mutagenesis to be independent of rate, the half-life of 2-aminoanthracene was seen to be less than approx 12 min (Author abstract) (15 Refs)

77. CYTOCHROME P-450-DEPENDENT MONOOXYGENASES IN OLFACTORY EPITHELIUM OF DOGS: POSSIBLE ROLE IN TUMORIGENICITY.

Dahl AR, Hadley WM, Hahn FF, Benson JM, McClellan RO

Inhalation Toxicology Res. Inst., Lovelace Biomedical and Environmental Res. Inst., Albuquerque, NM, 87185

Science; 216(4541):57-59 1982

The respiratory tract epithelium of dogs, from the nose to the lungs, was examined for cytochrome P-450 and associated biotransformation activities. In the ethmoturbinates, where olfactory epithelium is located, the amount of cytochrome P-450 was comparable to that in the liver, when measured on the basis of activity per milligram of microsomal protein. The rest of the nasal region also contained large quantities of cytochrome P-450. The presence of these enzymes in the nose may be important in chemical-induced tumorigenesis. The nasal carcinogen hexamethyl-phosphoramide was shown to be metabolized by nasal microsomal enzymes to another nasal carcinogen, formaldehyde. (Author abstract) (19 Refs)

78. THE CYTOCHROME P-450-DEPLETED ANIMAL: AN EXPERIMENTAL MODEL FOR IN VIVO STUDIES IN CHEMICAL BIOLOGY.

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Proc Nat. Acad Sci USA; 79(7):2384-2388 1982

An experimental method is described to deplete markedly in vivo the cytochrome P-450 content of liver for prolonged periods of time. The method uses the synthetic metalloporphyrin cobalt-heme (cobalt protoporphyrin IX), which possesses the dual biological properties of repressing delta-aminolevulinate synthase, the rate-limiting enzyme of heme biosynthesis, and of potently inducing microsomal heme oxygenase, the rate-limiting enzyme of heme catabolism. A single dose of cobalt-heme (125 umol/kg of body weight) decreased within 48 hr hepatic cytochrome P-450 to approx 20% of normal, at which level it remained for 10 days; normal levels were not achieved by 36 days. Periodic administration (total, 6 injections) of a smaller dose of cobalt-heme (50 umol/kg of body weight) maintained the cytochrome P-450 content at levels approx 15% of normal for greater than 90 days with concurrent profound impairment of mono-oxygenase reactions catalyzed by this heme protein. The ability of cobalt-heme to produce profound and prolonged depletion of cytochrome P-450 in vivo provides a valuable model for examining the role of cytochrome P-450-dependent metabolism in the biology of endogenous and exogenous chemicals. (Author abstract) (28 Refs)

ALTERATION OF OTHER CARCINOGEN-METABOLIZING ENZYMES BY CARCINOGENS

79. ALPHA-FETOPROTEIN FORMATION AND BIOCHEMICAL CHANGES IN RAT LIVER DURING N-DIMETHYLNITROSAMINE-INDUCED CARCINOGENESIS.

Dolezhalova V, Strasil P, Simickova M, Cherni S, Rubenchik BL, Pliss MB, Gorbar' GP
Inst. Clinical and Experimental Oncology, Brno, Czechoslovakia
Eksp Onkol; 4(1):51-55 1982

The effects of dimethylnitrosamine (DMNA) on the biosynthesis of alpha-fetoprotein (AFP) and liver metabolism were studied in male Wistar rats. Animals received a diet containing 0.01% DMNA for 20 wk. Extremely low blood levels of AFP were detected on wk 3-4, 25-26, and 35-36 after the initiation of DMNA administration. The low blood level of AFP was correlated with small number of hepatocytes containing AFP. AFP-positive hepatocytes were detected during the first wk after DMNA administration. The number of AFP-containing hepatocytes reached the max 30 wk after the initiation of the experiment, ie during the period of tumor development. The increase of deoxycytidylate deaminase activity was correlated with the increase of the proliferative activity of liver cells. Marked decrease of glucose-6-phosphatase was observed throughout the entire period of DMNA administration. DMNA did not change the rate of glycolysis or the activity of key glycolytic enzymes. (26 Refs) (In RUS)

80. COMPARISON OF ENHANCEMENT OF GGTASE-POSITIVE FOCI AND INDUCTION OF ORNITHINE DECARBOXYLASE IN RAT LIVER BY BARBITURATES.

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Carcinogenesis; 3(2):147-150 1982

The induction of ornithine decarboxylase (ODC) by barbiturates and the ability of barbiturates to enhance neoplastic progression of chemically initiated cancer was examined in rat liver. All seven barbiturates induced ODC with barbital (7.7 fold increase) and phenobarbital (5.7 fold increase) demonstrating the most potent activity. Maximum induction of ODC by phenobarbital was obtained in 18 h. Barbital (500-5,000 ppm) and phenobarbital (500 ppm) administered in the drinking water enhanced the appearance of diethylnitrosamine (DENA)-initiated gamma-glutamyltranspeptidase (GGTase)-positive foci. Amobarbital, hexabarbital and pentobarbital did not enhance the appearance of GGTase-positive foci. In the absence of previous initiation by DENA, the enhancing regimen of the barbiturates did not cause the appearance of GGTase-positive foci. Barbiturates induced ODC activity in rat liver and enhanced the incidence of DENA initiated GGTase-positive foci. (Author abstract) (24 Refs)

81. EARLY CHANGES IN MITOCHONDRIAL MONOAMINE OXIDASE ACTIVITY OF RAT LIVER DURING HEPATOCARCINOGENS FEEDING.

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Excerpta Med Int Congr Ser; 564():241-250 1982

The effects of 3'-methyl-4-dimethylaminoazobenzene (3'-Me-DAB), 2-acetylamino-fluorene (2-AAF), 2-aminofluorene (2-AF), 2-nitrofluorene (2-NF), and N-hydroxy-2-AAF on mitochondrial monoamine oxidase (MAO) activity of rat liver are reported. Male and female Donry rats were used. Significant decrease (70%) in MAO-B activity was observed during 3'-Me-DAB feeding. The changed patterns of MAO-B activity are similar to those of rat hepatoma. When rats were fed a diet containing 0.05% 2-AAF, a remarkable decrease of MAO-B activity was observed, while MAO-A activity was not affected. In female rats fed 0.05% 2-AAF diet, MAO-B activity was not changed after 1 wk, but decreased to some extent at 3 and 12 wk after the exposure to the carcinogen. The intensity of the MAO-B activity decrease in female rats was to a lesser extent as compared to that of male rats at each time period. 2-AAF higher concentrations inhibited MAO-B activity when added in vitro, but MAO-A activity was strongly inhibited by addition of 10(-7) M 2-AAF. Each compound of fluorene derivatives tested was administered po at a dose of 200 micromoles/kg daily for 7 days. N-hydroxy-2-AAF and 2-AF decreased MAO-B activity. 2-NF did not show any effect under experimental conditions. Effect of 2-AAF on MAO-B activity was examined in thyroxine-treated and riboflavin-deficient rats. An additive decrease of MAO-B activity was observed in 2-AAF and thyroxine-treated animals as compared to the decrease produced by the separate administration. When rats were fed riboflavin-deficient diet for 2 wk, MAO-B activity was decreased to 60% of the control levels. The decreased activity tended to return to control levels if rats were fed the basal diet again. (27 Refs)

82. EFFECT OF PROCARBAZINE TREATMENT OF MICE ON ALPHA-GLYCEROLPHOSPHATE DEHYDROGENASE ACTIVITY AND FREQUENCY OF SELECTED ABNORMALITIES IN SPERM.

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Mutat Res; 92(1/2):249-256 1982

Male DBA/2J mice (10-12 wk old) were given one ip dose of procarbazine (PCB: 0-800 mg/kg). Levels of mitochondrial alpha glycerol phosphate dehydrogenase (a-GPD) in the sperm and the frequencies of two specific sperm abnormalities (headlessness and PL-type disorganization of the mitochondrial assembly) were studied 4-55 days after treatment. PCB caused dose-related increases in the frequencies of sperm without active a-GPD and/or morphologically abnormal spermatozoa. The lowest dose causing the abnormalities was 200 mg/kg. Individual variations in response to each dose of PCB were observed. Since quantifiable changes in mitochondrial a-GPD activity were easily detected at 200 mg/kg of PCB, the measurement may be a useful indicator of a chemical agent's ability to reach the germinal tissue in an active and possibly mutagenic form. No abnormalities of spermatic morphology or a-GPD were observed 85 days after PCB administration. (14 Refs)

83. DISTRIBUTION OF 5'-NUCLEOTIDASE DURING HEPATOCARCINOGENESIS INDUCED BY HEXACHLOROCYCLOHEXANE IN SWISS MICE.

Bhatt DK, Nigam SK, Lakkad BC, Babu KA, Karnik AB, Thakore KN, Kashyap SK, Chatterjee SK
Natl. Inst. Occupational Health (ICMR), Meghani Nagar, Ahmedabad 380 016, India
Indian J Exp Biol; 19(12):1159-1162 1981

Male inbred Swiss mice were fed 500 ppm of hexachlorocyclohexane (BHC) for 2, 4, or 6 mo and the livers were histochemically studied for the distribution of 5'-nucleotidase (5NT). After 2 mo, hepatocytes in the periportal area showed intense enzymatic activity. Activity in the nodular part increased compared with the nonnodular part. Tumor tissue always showed very strong 5NT activity compared with the nontumor tissue. Intercellular spaces showed strong 5NT activity. As time increased, the main changes in 5NT distribution were disappearance of 5NT from the cytoplasm (persisting even after tumor development), increase in 5NT activity in the nucleus (disappearing in well developed nodules and tumors) and gradual increase in 5NT activity on the plasma membrane and intercellular space. The change in activity during hepatocarcinogenesis may be associated with the functional and constitutional aspect of the plasma membrane. The absence of cytoplasmic activity of 5NT may be associated with complete disruption of ergestroplasm during carcinogenesis, excessive accumulation of glycogen in the cytoplasm, lysosomal damage, and repression of the gene responsible for synthesis of cytoplasmic 5NT. 5NT may be a specific indicator of hepatic diseases and tumors of the liver. (22 Refs)

84. INDUCTION OF ORNITHINE DECARBOXYLASE IN COLON AND LIVER BY STARVATION AND REFEEDING: A COMPARISON OF EFFECTS ON TOTAL AND HOLOENZYME.

Stanley BA, Kazarinoff M
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Biochem Biophys Res Commun; 105(2):773-777 1982

Short-term starvation and refeeding induced both the total and holo-ornithine decarboxylase (ODC) levels in the colon of rats. After brief starvation alone, a significant decrease in total ODC was observed in the colon; there was no effect on colon holo-ODC. Similar effects on total ODC level were seen in the liver; neither starvation-refeeding nor starvation alone had any effect on liver holo-ODC levels. This is the first demonstration of the dietary induction of ODC in the colon. It is of interest to investigate whether this induction simply reflects a compensatory increase in general protein synthesis following starvation, or whether it represents a specific induction such as that observed during tumor promotion by chemical carcinogens. (18 Refs)

REVIEWS AND OTHER RELEVANT STUDIES

85. THE MECHANISM OF ACTION OF CARCINOGENS AND TUMOR PROMOTERS AND THEIR RELEVANCE TO CANCER PREVENTION.

Weinstein IB
Div. Environmental Sciences, Columbia Univ. Coll. Physicians and Surgeons, New York, NY, 10032
Cancer Research in the People's Republic of China and the United States of America: Epidemiology, Causation and New Approaches to Therapy. Proceedings of a Conference held in New York, 28-29, March, 1980. Marks PA, ed. New York, Grune and Stratton, 273 pp., 1981.

Systems for studying malignant cell transformation in vitro, mimicry of transformation, modulation of differentiation, membrane effects and phospholipid metabolism, membrane receptors for epidermal growth factor and 12-O-tetradecanoyl-phorbol-13-acetate (TPA), synergistic interactions between chemical agents and viruses in cell transformation, molecular mechanism of initiation, and a unified theory of initiation and promotion are discussed. Examples of cell culture systems that can be transformed by chemical carcinogens and by TPA modulation of differentiation are presented. (61 Refs)

86. MODIFICATIONS OF CHROMATIN STRUCTURE IN CONTROL OF GENE EXPRESSION.

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Med Hypotheses; 8(2):113-133 1982

The mechanisms controling gene expression and cellular differentiation in higher eukaryotic organisms are an active area of research in molecular biology. This article reviews what is known about chromatin structure and its regulations, and the following aspects are included the basic building block - the nucleosome,; the histone and nonhistone proteins which maintain chromosome structure and control transcription, the replication and transcription enzymes, repetitive sequences in DNA, DNA introns, and chromosomal RNA. A number of chromatin modifications such as DNA methylation and phosphorylation-dephosphorylation or acetylation-deacetylation of chromosomal proteins, and apparently involved in the control of gene expression are discussed. Tumor viruses and carcinogens may cause changes in chromatin structure resulting in a circumvention of normal cell cycle controls of proliferation. (68 Refs)

87. ABSENCE OF MUTAGENIC ACTIVITY OF THREE FORMS OF ASBESTOS IN LIVER EPITHELIAL CELLS.

Reiss B, Solomon S, Tong C, Levenstein M, Rosenberg SH, Williams GM
Naylor Dana Inst. Disease Prevention, American Health Foundation, 1 Dana Road, Valhalla, NY, 10595
Environ Res; 27(2):389-397 1982

The amosite, crocidolite, and chrysotile forms of UICC asbestos were assayed for their ability to induce gene mutations at the hypoxanthine-guanine phosphoribosyl transferase locus. Using adult rat liver-derived (ARL-6 and ARL-18) cells in culture, no consistent or significant increase occurred in the number of mutants resistant to the purine analog, 6-thioguanine, after exposure to toxic levels of amosite, crocidolite, or chrysotile. These results support the concept that asbestos is an epigenetic carcinogen that does not alter DNA. (Author abstract) (55 Refs)

88. IS COFFEE DRINKING A HEALTH HAZARD?

Chaudhuri MM, Ghosh S
Botany Dept., Bose Inst., Calcutta 700009, India
Sci Culture; 47(5):157-160 1981

Whether caffeine or its derivatives is a health hazard is discussed with respect to chemistry, metabolism, and mutagenicity testing. Evidence suggests that caffeine at low doses may act as a stimulator of the nervous system. High consumption, particularly in pathological conditions, may be hazardous. The dose [illegible] caffeine required for embryotoxicity is [illegible]00 mg/kg (equi[illegible]ent to 40 cups of coffee). Mutagenicity testing has led to various conflicting results: caffeine has been found to be nonmutagenic, comutagenic, or a potent mutagen, particularly at high doses. (44 Refs)

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CHEMICAL CARCINOGENESIS

1. TOXICITY AND METABOLISM OF ACRYLONITRILE.
Sapota A, Chmielnicka J
Zaklad Metabolizmu Substancji Toksycznych, Instytut Medycyny Pracy, ul. Teresy 8, 90-950 Lodz, Poland
Med Pr; 32(1):25-33 1981
In POL

2. A REVIEW OF THE GENOTOXICITY OF FOOD, DRUG AND COSMETIC COLOURS AND OTHER AZO, TRIPHENYLMETHANE AND XANTHENE DYES.
Combes RD, Haveland-Smith RB
Dept. Biological Sciences, Portsmouth Polytechnic, King Henry I St., Portsmouth, PO1 2DY, Hants, England
Mutat Res; 98(2):101-248 1982

3. CARCINOGENICITY OF AIRBORNE FINE PARTICULATE BENZO(A)PYRENE: AN APPRAISAL OF THE EVIDENCE AND THE NEED FOR CONTROL.
Perera F
Natl. Resources Defense Council, Inc., 122 East 42nd St., New York, NY, 10168
Environ Health Perspect; 42:163-185 1981

4. TOXICOLOGY OF N-NITROSO COMPOUNDS.
Coulston F, Olajos EJ
Albany Medical Coll., Albany, NY, 12208
Ecotoxicol Environ Saf; 6(1):89-96 1982

5. CRITICAL REVIEW OF THE MUTAGENIC AND OTHER GENOTOXIC EFFECTS OF DIRECT COAL LIQUEFACTION.
Kimball RF, Munro NB
Oak Ridge Natl. Lab., Oak Ridge, TN
Critical Review of the Mutagenic and Other Genotoxic Effects of Direct Coal Liquefaction. Available from National Technical Information Service, Springfield, VA, as DE81027859., 216 pp., 1981.

6. CARCINOGENICITY AND ITS EFFECT ON MEDICINAL RESEARCH PROGRAMS IN THE USA.
Van Ryzin RJ
Pharmaceutical Res. and Development, Sandoz, Inc., East Hanover, NJ, 07936
Med Res Rev; 2(2):153-166 1982

7. ANTIPROTOZOAL DRUGS (SIDE EFFECTS).
Nir I
Dept. Pharmacology and Experimental Therapeutics, The Hebrew Univ., Hadassah Medical Sch., Jerusalem, Israel
Side Eff Drugs Annu; (5):278-284 1981

8. DRUGS USED IN TUBERCULOSIS AND LEPROSY (SIDE EFFECTS).
Elis J
Inst. Pharmacology, Czechoslovak Acad. Sciences, Albertov 4, Prague 2, Czechoslovakia
Side Eff Drugs Annu; (5):290-297 1981

9. SEX HORMONES AND RELATED COMPOUNDS, INCLUDING ORAL CONTRACEPTIVES.
Plotz EJ, Nocke W, Schander K, Patt V, Kaulhausen H
Dept. Obstetrics and Gynecology, Univ. Bonn, 5300 Bonn-Venusberg, W. Germany
Side Eff Drug Annu; (5):358-380 1981

RADIATION CARCINOGENESIS

10. NEPTUNIUM - THE NEGLECTED ACTINIDE: A REVIEW OF THE BIOLOGICAL AND ENVIRONMENTAL LITERATURE.
Thompson RC
Biology Dept., Pacific Northwest Lab., Richland, WA, 99352
Radiat Res; 90(1):1-32 1982

11. CARCINOGENIC EFFECT OF RADIOACTIVE PRODUCTS.
Vasilenko IIa
No affiliation given
Vopr Onkol; 28(1):76-83 1982
In RUS

DIETARY FACTORS IN CARCINOGENESIS

12. FIBRES, NUTRITION AND THE GUT.
Sramijver M, Tytgat GN
Dept. Internal Medicine, Div. Gastroenterology, Univ. Amsterdam, 1e Helmersstraat 104, 1054 EG Amsterdam, The Netherlands
Neth J Med; 25(2):49-55 1982

13. DIETARY FIBER AND DISEASE.
Kritchevsky D
Wistar Inst. Anatomy and Biology, Philadelphia, PA
Bull NY Acad Med; 58(3):230-241 1982

14. ASSESSING HUMAN EPIDEMIOLOGIC DATA ON DIET AS AN ETIOLOGIC FACTOR IN CANCER DEVELOPMENT.
Enstrom JE
Sch. Public Health, Univ. California, Los Angeles, CA
Bull NY Acad Med; 58(3):313-322 1982

15. NUTRITION AND CANCER: MECHANISMS OF GENOTOXIC AND EPIGENETIC CARCINOGENS IN NUTRITIONAL CARCINOGENESIS.
Weisburger JH, Horn C
American Health Foundation, Valhalla, NY, 10595
Bull NY Acad Med; 58(3):296-312 1982

EPIDEMIOLOGY, ETIOLOGY AND GENETIC ASPECTS OF HUMAN CANCER

16. THE AH LOCUS, A MULTIGENE FAMILY NECESSARY FOR SURVIVAL IN A CHEMICALLY ADVERSE ENVIRONMENT: COMPARISON WITH THE IMMUNE SYSTEM.
Nebert DW
Developmental Pharmacology Branch, National Inst. Child Health, NIH, Bethesda, MD, 20205
Adv Genet; 21:1-52 1982

ENVIRONMENTAL AND OCCUPATIONAL FACTORS IN CARCINOGENESIS

17. SKIN CANCER: OCCUPATIONAL CAUSES.
Bickers DR
Dept. Dermatology, Case Western Reserve Univ., Cleveland, OH
Consultant; 22(4):392-393,397,400-401 1982

18. OCCUPATIONAL AND ENVIRONMENTAL HEALTH PROBLEMS OF THE DEVELOPING OIL SHALE INDUSTRY: A REVIEW.
Rom WN, Lee JS, Craft BF
Rocky Mountain Center Occupational and Environmental Health, Dept. Internal Medicine, Family and Community Medicine, Univ. Utah Sch. Medicine, Bldg. 512, Salt Lake City, UT 84112
Am J Industr Med; 2(3):247-260 1981

19. POLYCYCLIC AROMATIC HYDROCARBONS IN THE OCCUPATIONAL ENVIRONMENT: WITH SPECIAL REFERENCE TO BENZO[A]PYRENE MEASUREMENTS IN SWEDISH INDUSTRY.
Lindstedt G, Sollenberg J
Chemistry Dept., Natl. Board Occupational Safety and Health, S-171 84 Solna, Sweden
Scand J Work Environ Health; 8(1):1-19 1982

20. GENETIC RISKS AND ENVIRONMENTAL SURVEILLANCE: EPIDEMIOLOGICAL ASPECTS OF MONITORING INDUSTRIAL POPULATIONS FOR ENVIRONMENTAL MUTAGENS.
Buffler PA, Aase JM
Sch. Public Health, Univ. Texas Health Science Center at Houston, P.O. Box 20186, Houston, TX, 77025
JOM; 24(4):305-314 1982

21. OSHA AT THE THRESHOLD: SETTING PERMISSIBLE EXPOSURE LEVELS FOR KNOWN CARCINOGENS AFTER AMERICAN PETROLEUM INSTITUTE.
Blackmar GB
No affiliation given
San Diego Law Rev; 18(4/5):633-661 1981

22. CARCINOGENESIS: PROBLEMS AND PARADOXES. THE 1981 GEORGE H. GEHRMANN LECTURE.
Kotin P
4505 South Yosemite, 339, Denver, CO, 80237
JOM; 24(4):291-294 1982

CELLULAR AND MOLECULAR MECHANISMS IN CARCINOGENESIS

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Hull LA
104 Depot St., New Sharon, IA, 50207
Med Hypotheses; 8(2):113-133 1982

24. PLASMINOGEN ACTIVATORS IN NEOPLASTIC CELLS.
Goloborod'ko OP, Vetroseenko KN
A. I. Kolomiichenko Res. Inst. Otolaryngology, Kiev, USSR
Eksp Onkol; 4(1):3-7 1982
In RUS

25. TUMOR PROMOTION BY REGENERATIVE EPIDERMAL HYPERPLASIA IN MOUSE SKIN.
Argyris TS
Dept. Pathology, Upstate Medical Center, State Univ. New York, Syracuse, NY, 13210
J Cutan Pathol; 9(1):1-18 1982

26. SEX HORMONES AND LIVER CANCER.
Williams GM
Naylor Dana Inst. for Disease Prevention, New York Medical Coll., Valhalla, NY
Lab Invest; 46(3):352-354 1982

METHODOLOGY IN CARCINOGENESIS RESEARCH

27. UTILIZATION OF CELL TRANSFORMATION TESTS IN THE DETECTION OF CHEMICAL CARCINOGENS.
Elias Z, Cavelier C
Institut National de Recherche, Centre de Recherche de Nancy, avenue de Bourgogne, F 54500 Vandoeuvre-les-Nancy, France
Bull Cancer (Paris); 69(1):33-57 1982
In FRE

28. FAILURES AND CRITIQUE OF THE BEIR III LUNG CANCER RISK ESTIMATES.
Cohen BL
Univ. Pittsburgh, Pittsburgh, PA, 15260
Health Phys; 42(3):267-284 1982

OTHER REVIEWS IN CARCINOGENESIS

29. CANCER: AN INTRODUCTION.
Creasey WA
Dept. Pharmacology, Univ. Pennsylvania Sch. Medicine, Philadelphia, PA
Cancer: An Introduction. New York, Oxford University Press, 271 pp., 1981

30. CANCER 1980: ACHIEVEMENTS, CHALLENGES, AND PROSPECTS.
Clark RL
Univ. Texas System Cancer Center, M.D. Anderson Hosp. and Tumor Inst., 6723 Bertner Ave., Houston, TX, 77030
Cancer; 49(9):1739-1745 1982

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Activation and Metabolism of Carcinogens

SERIES CK08 No. 82/09

SEPTEMBER, 1982

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
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HE 20.3173/2:

METABOLIC ACTIVATION OF CARCINOGENS

1. FORMATION OF THE 11,12-DIOL AS A METABOLITE OF BENZO(A)PYRENE BY RAT SKIN IN VIVO.

Weston A, Grover PL, Sims P
Chester Beatty Res. Inst., Royal Cancer Hosp., Fulham Road, London SW3 6JB, England
Biochem Biophys Res Commun; 105(3):935-941 1982

Identification of the 11,12-diol metabolite of benzo(a)pyrene (BP) in rat skin that had been exposed to 3H-BP in vivo is described. High pressure liquid chromatographic analysis revealed that each of the four possible dihydrodiols were formed after application of BP to rat skin. Similar application of BP to mouse skin, however, resulted in the formation of only the 4,5-, 7,8-and 8,10-diols. These findings agree with previous in vitro work. The formation of only two or three dihydrodiols as a result of BP metabolism in a large number of tissues may be indicative of mono-oxygenase specificity, since four dihydrodiols including the 11,12-diol are formed by oxidation in an ascorbic acid-ferrous sulfate-EDTA system and both K-region double bonds can be attacked by osmium tetroxide. The possibility exists that BP-11,12-oxide is formed but is removed through conjugation with glutathione, or that BP-11,12-diol is formed but is removed through reaction with glucuronyltransferase or sulfotransferase. However, the 11,12-diol has been identified in vivo. Variations in metabolism and detoxification may be linked with the relative resistance of rat skin to BP carcinogenesis. (27 Refs)

2. MICROSOMAL METABOLISM OF 8-FLUOROBENZO[A]PYRENE (MEETING ABSTRACT)

Chou MW
National Center for Toxicological Research, Jefferson, AR, 72079
Fed Proc; 41(3):1573 1982

Fluorobenzo[a]pyrene (8-FBP) is a more potent mutagen than benzo[a]pyrene (BP) in Salmonella typhimurium tester strain TA 98 and TA 1538 with S9 or microsome activation. Metabolism of 8-FBP by rat liver microsomes was studied to elucidate the activation pathways. The major metabolites formed were purified by high performance liquid chromatography and identified as 3-hydroxy-8-FBP, 3,x-dihydroxy-8-FBP and 8-FBP-trans-4,5-dihydrodiol by the analyses of uv, mass and nmr (nuclear magnetic resonance) spectra. The circular dichroism spectrum of 8-FBP-trans-4,5-dihydrodiol was similar to that of BP-4R,5R-dihydrodiol, a metabolite of BP, indicating that 8-FBP-trans-4,5-dihydrodiol also has a 4R,5R absolute configuration. The results suggest that a fluoro substituent at C-8 of BP (1) can inhibit the enzymatic oxidation at the 7,8-and 9,10-positions but (2) does not change the stereospecificities of the cytochrome P-450 enzymes and of epoxide hydrolase for 8-FBP-trans-4R,5R-dihydrodiol formation. The results also suggest that 8-FBP-4,5-oxide, the precursor of 8-FBP-trans-4,5-dihydrodiol, may be an ultimate mutagenic metabolite of 8-FBP. (no Refs)

3. METABOLISM OF THE MUTAGENIC ENVIRONMENTAL POLLUTANT, 6-NITROBENZO[A]PYRENE: METABOLIC ACTIVATION VIA RING OXIDATION.

Fu PP, Chou MW, Yang SK, Beland FA, Kadlubar FF, Casciano DA, Heflich RH, Evans FE
Natl. Center for Toxicological Res., Jefferson, AR, 72079
Biochem Biophys Res Commun; 105(3):1037-1043 1982

The effect of 6-nitro substitution on the metabolic activation of the parent compound, benzo(a)pyrene, and on mutagenic activation in the Salmonella typhimurium/microsome reversion assay was investigated. Separation of 6-nitro-BP metabolites was effected using reversed-phase high pressure liquid chromatography. The monohydroxylated 6-nitro-BP metabolites were the most active mutagens in the Ames assay, suggesting that these compounds were the proximal mutagens. (16 Refs)

4. A STUDY OF STERIC AND ELECTRONIC FACTORS GOVERNING THE POSITION OF BIOFUNCTIONALIZATION OF THE BENZ(A)ANTHRACENE OF THE BENZ(A)ANTHRACENE NUCLEUS: METABOLISM IN VITRO OR FLUORO- AND METHYL-SUBSTITUTED ANALOGS.

Sheikh YM, Hart RW, Witiak DT
Div. Medicinal Chemistry and Pharmacognosy, Coll. Pharmacy, Comprehensive Cancer Center, Ohio State Univ., Columbus, OH, 43210
Bioorg Chem; 10(4):429-442 1981

The metabolism of benz(a)anthracene (BA) analogs having fluoro groups (positions 3, 5, or 6) and/or methyl groups (positions 7 or 12) and of 7,12-dimethylbenz(a)anthracene analogs having fluoro groups (positions 2, 3, 4, 5, or 6) was studied in rat liver microsome (S-10) fractions induced by phenobarbital, beta-naphthoflavone, or 3-methylcholanthrene. Assays of the metabolites produced from these substrates (notably the dihydrodiol metabolites) suggested that both steric and electronic factors may determine the preferential sites of bioactivation of the BA and DMBA analogs. A hypothesis is presented to account for these findings. (42 Refs)

5. METABOLISM OF PHENANTHRENE IN VARIOUS MARINE ANIMALS.

Solbakken JE, Palmork KH
Inst. Marine Res., Directorate of Fisheries, Nordnesparken 2, N-5011 Bergen, Norway
Comp Biochem Physiol [C]; 70(1):21-26 1981

Metabolites of phenanthrene (PA) were analyzed by combined gas chromatography-mass spectroscopy in tissues of flounder (Platichthys flesus), rainbow trout (Salmo gairdneri), spiny dogfish (Squalus acanthias), and Norway lobster (Nephrops norvegicus), which had been force fed PA at a rate of 21-357 mg/kg. Fish and crustaceans are able to metabolize PA to water-soluble conjugated and non-conjugated metabolites, which vary by species and in tissue distribution. (24 Refs)

6. METABOLIC NITRITE FORMATION FROM N-NITROSAMINES: EVIDENCE FOR A CYTOCHROME P-450 DEPENDENT REACTION.

Appel KE, Graf H
Section Toxicology, Inst. Pharmacology, Obere Zahlbacher Str. 67, D-6500 Mainz, W. Germany
Carcinogenesis; 3(3):293-296 1982

Nitrite was formed on incubation of N-nitrosamines with a reconstituted monooxygenase system, consisting of cytochrome P-450 (P-450) and NADPH P-450 reductase from pig liver. Nitrite was not obtained when the nitrosamines were incubated with NADPH P-450 reductase alone or when molecular oxygen or NADPH were omitted. Interaction of nitrosamines with the reconstituted P-450 system or with hemoglobin under reducing conditions resulted in optical spectra identical with those obtained with nitrite. It is proposed that N-nitrosamines are denitrosated by electron transfer from the hemoprotein iron to the nitrosamine molecule. (Author abstract) (27 Refs)

7. RELATIONSHIP BETWEEN CARCINOGENICITY AND IN VITRO METABOLISM OF NITROSOMETHYLETHYLAMINE, NITROSOMETHYL-N-BUTYLAMINE, AND NITROSOMETHYL(2-PHENYLETHYL)AMINE LABELED WITH DEUTERIUM IN THE METHYL AND ALPHA-METHYLENE POSITIONS.

Farrelly JG, Stewart ML, Saavedra JE, Lijinsky W

Chemical Carcinogenesis Program, NCI-Frederick Cancer Res. Facility, Frederick, MD, 21701

Cancer Res; 42(6):2105-2109 1982

With the use of rat liver preparations, the in vitro microsomal metabolism of methylethylnitrosamine, methyl-n-butylnitrosamine, and methyl(2-phenylethyl)nitrosamine labeled with deuterium in the methyl and alpha-methylene positions has been compared with that of the parent (unlabeled) compounds. All three forms of the liver carcinogen methylethylnitrosamine are metabolized with two sets of kinetic constants. Examination of these kinetic constants suggests that both methylation and ethylation of cellular nucleophiles might be important in the carcinogenic action of these nitrosamines. The esophageal carcinogen, methyl(2-phenylethyl)nitrosamine, gave only one set of kinetic constants during metabolism. The metabolism of the three methylbutylnitrosamines gave results similar to that of the three methylethyl nitrosamines. Except for metabolism of d2-methylbutylnitrosamine to butyraldehyde, two sets of kinetic constants were found. Approximately equivalent amounts of methylating species were produced from d3-methylbutylnitrosamine and d0-methylbutylnitrosamine. (Author abstract) (16 Refs)

8. ESOPHAGEAL CARCINOGENESIS IN F344 RATS BY NITROSOMETHYLETHYLAMINES SUBSTITUTED IN THE ETHYL GROUP.

Lijinsky W, Saavedra JE, Reuber MD, Singer SS

Chemical Carcinogenesis Program, NCI-Frederick Cancer Res. Facility, P.O. Box B, Frederick, MD, 21701

JNCI, 68(4):681-684 1982

The carcinogenic activity in male F344 rats of five nitrosomethylalkylamines related to nitrosomethylethylamine has been examined. All rats were tested by administration of controlled doses of the compounds in the drinking water. Nitrosomethylbenzylamine was the most potent carcinogen of the five, causing death of most animals with tumors of the upper gastrointestinal tract (mainly the esophagus) within 6 mo after a total dose of 0.2 mmol. The remaining compounds, all of which can be considered true derivatives of nitrosomethylethylamine, were less potent than nitrosomethylbenzylamine but also induced a high incidence of tumors of the esophagus. Nitrosomethyl-2-phenylethylamine and nitrosomethylneopentylamine were of comparable potency, while nitrosomethyltrifluoroethylamine was considerably less potent, as measured by the time to death with esophageal tumors. Deuterium-labeled nitrosomethylethylamine, in which deuterium replaces hydrogen on the beta-carbon atom of nitrosomethylethylamine, induced a high incidence of esophageal tumors as well as liver tumors after administration of identical doses. Reactions on the beta-carbon atom of nitrosomethylethylamine might be important as well as oxidation at the alpha-carbon atoms in determining carcinogenic effects. (Author abstract) (16 Refs)

9. RAT MAMMARY GLAND CARCINOGENESIS AFTER LOCAL INJECTION OF N-HYDROXY-N-ACYL-2-AMINOFLUORENES: RELATIONSHIP TO METABOLIC ACTIVATION.

Allaben WT, Weeks CE, Weis CC, Barger GT, King CM

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Carcinogenesis; 3(3):233-240 1982

A single local injection of 2.5 μmol of N-hydroxy-N-formyl-2-aminofluorene (N-hydroxy-FAF), N-hydroxy-N-acetyl-2-aminofluorene (N-hydroxy-AAF), or N-hydroxy-N-propionyl-2-aminofluorene (N-hydroxy-PAF) to each of the six left mammary glands of female Sprague-Dawley derived CD rats gave a mammary tumor incidence, after 12 mo, of 53% for the N-acetyl, 41% for the N-formyl and 35% for the N-propionyl derivatives of N-hydroxyl-N-2 aminofluorene. When N-acetyl-2-aminofluorene (AAF) was applied as above there was only an 8% mammary tumor incidence. Arylhydroxamic acid N,O-acyltransferase activity has been demonstrated in the mammary glands of male, and lactating and non-lactating female Sprague-Dawley derived CD rats by means of a nucleic acid binding assay. Mammary gland cytosol catalyzed tRNA adduct formation to a greater extent with N-hydroxy-FAF. AAF was not activated by this enzyme. Ammonium sulfate fractionation demonstrated the presence of two enzymes, one specific for N-hydroxy-FAF, the other specific for N-hydroxy-AAF and N-hydroxy-PAF. Gel filtration chromatography of mammary gland cytosol demonstrated the presence of two enzymes of differing acyl specificity. Mammary gland microsomes catalyzed the formation of tRNA adducts, but only with the N-hydroxy-FAF derivative. Assays that tested the mutagenic potential of the arylhydroxamic acids in Salmonella typhimurium TA-1538 with either mammary gland cytosol or microsomes demonstrated the order of mutagenicity to be N-hydroxy-FAF much greater than N-hydroxy-AAF greater than N-hydroxy-PAF. A similar order of mutagenicity was demonstrated without an external metabolic activation system. These data demonstrate the presence of two distinct enzymes in the rat mammary gland that activate arylhydroxamic acids. (37 Refs)

10. STUDIES ON METABOLISM AND TOXICITY OF STYRENE. V. THE METABOLISM OF STYRENE, RACEMIC (R)-(+)-, AND (S)-(-)-PHENYLOXIRANES IN THE RAT.

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J Pharmacobio Dyn; 5(2):129-133 1982

The stereochemical course of in vivo metabolism of styrene and optically active phenyloxiranes through the hydrolysis and conjugation routes was studied. (R)-(-)- and (S)-(+)-phenylethanediols and (R)-(+)- and (S)-(-)-phenyloxiranes with enantiomeric purities greater than 99% were synthesized and injected ip into rats at 2 millimole/kg, and urine specimens were examined for metabolites over a 24-hr period. The process was repeated for each compound in turn at weekly intervals. Evidence suggests that styrene, racemic phenyloxirane, and its (S)-isomer are metabolized via the hydrolysis route, and that the (R)-isomer is converted mainly to mercapturic acids via the conjugation route. Administration of styrene, racemic phenyloxirane, or its optically pure isomers leads to predominant formation of the mercapturic acid isomer MA-1, over the other regioisomer MA-2. A very large portion of injected styrene was metabolized via the mutagenic phenyloxirane to nontoxic compounds. (23 Refs)

11. MAJOR APPROACHES TO THE EXPERIMENTAL STUDY OF LUNG CANCER.

Pliss GB, Turusov VS, Zabezhinskii MA
No affiliation given
Vopr Onkol; 28(2):18-22 1982

Experimental models used in the study of the etiology and pathogenesis of lung cancer are reviewed. The experimental lung tumors should meet following requirements: ease of induction, high selectivity and reproducibility, and similarity with human tumors with respect to the morphology and clinical manifestations. Metabolism of various carcinogens was studied in organ cultures of human bronchi. Experiments in nude mice subjected to sc implantation of the fragments of human bronchi and administration into the transplants of the pills containing 7,12-dimethylbenz(a)anthracene or 3-methylcholanthrene provided additional data on the sensitivity of bronchial epithelium to various carcinogens and the characteristic features of different stages of carcinogenesis. Experimental models confirmed the role of chronic lung diseases in the etiology of lung cancer. Experimental studies of the dose-effect curves during pulmonary carcinogenesis induced by polycyclic hydrocarbons provided the basis for the estimation of the maximum permissible levels of benzo(a)pyrene in the air. (20 Refs) (In RUS)

OTHER METABOLISM OF CARCINOGENS

12. FUNCTIONAL HETEROGENEITY OF UDP-GLUCURONOSYLTRANSFERASE ACTIVITIES IN C57BL/6 AND DBA/2 MICE.

Bock KW, Lilienblum W, Pfeil H
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Biochem Pharmacol; 31(7):1273-1277 1982

Functional heterogeneity of liver microsomal UDP-glucuronosyltransferase activities towards 1-naphthol, 4-methylumbelliferone or 3-hydroxybenzo(a)pyrene (UDP-GT1 activities) and morphine or 4-hydroxybiphenyl (UDP-GT activities) was studied in two inbred strains of mice which are genetically responsive (C57BL/6) or non-responsive (DBA/2) to methylcholanthrene-induction of drug metabolizing enzymes. 3-Methylcholanthrene preferentially induced UDP-GT1 activities in C57BL/6 mice. Phenobarbital, however, at low doses (50 mg/kg), selectively inhibited UDP-GT2 activities. Higher doses of phenobarbital (80 mg/kg) induced both UDP-GT1 and UDP-GT2 activities. In DBA/2 mice 3-methylcholanthrene-induction of UDP-glucuronosyltransferase activities was not detectable whereas enzyme induction by phenobarbital appeared to be unimpaired. UDP-GT1 activities were ubiquitously detectable in mouse tissues whereas appreciable UDP-GT2 activities were only found in liver and small intestinal mucosa. UDP-GT1 (1-naphthol as substrate) was not inhibited by morphine suggesting different active sites for the conjugation of these substrates. The results suggest the presence of at least two functionally different forms of UDP-glucuronosyltransferase in mice. In conjunction with the results of Owens it is evident that one of these enzyme forms is regulated by the Ah locus. (Author abstract) (38 Refs)

MODIFICATION OF CARCINOGEN METABOLISM

13. DIFFERENTIAL EFFECTS OF DIETARY ANTIOXIDANTS OF CHEMICAL CARCINOGENESIS (MEETING ABSTRACT)

King MM, McCay PB
Oklahoma Medical Research Foundation, Oklahoma City, OK. 73104
Fed Proc; 41(3):358 1982

Female weanling Sprague-Dawley rats were fed a defined semipurified diet with antioxidants being supplemented throughout the experiments as indicated. In one set of experiments, the diets were supplemented with butylated hydroxytoluene (BHT). The rats were given a 10 mg oral dose of 7,12-dimethylbenz(a)anthracene at 50 days of age. The incidence of mammary adenocarcinomas was markedly lower in the BHT-supplemented rats compared to rats fed the same diet without BHT. When butylated hydroxyanisole (BHA) was supplemented in the diet instead of BHT, no inhibition of mammary tumor development was observed. In similar experiments, it was found that propyl gallate supplementation also offers protection against DMBA-induced tumorigenesis while alpha-tocopherol does not. These results raise the question: is the antioxidant property of the supplement actually related to inhibition of tumorigenesis or is it some other property of particular antioxidants (in this case, BHT and propyl gallate)? To determine if BHT may possibly be affecting some metabolic system associated with the activation of DMBA to the ultimate carcinogen, the effect of BHT supplementation on tumor induction was compared between a direct acting mammary carcinogen (nitrosomethylurea) and DMBA, which does require metabolic activation. BHT inhibited DMBA- but not NMU-induced mammary tumorigenesis, suggesting that the influence of BHT may involve inhibition of DMBA activation. (no Refs)

14. EFFECT OF DIETARY PROTEIN ON INDUCTION OF 7,12-DIMETHYLBENZ(A)ANTHRACENE MUTAGENESIS BY RAT LIVER MICROSOMES IN THE SALMONELLA/MICROSOME TEST SYSTEM (MEETING ABSTRACT)

Singletary KW, Martin SE, Milner JA
Department of Food Science, University of Illinois, Urbana, IL, 61801
Fed Proc; 41(3):356 1982

Studies have shown that a high protein diet decreases the incidence of 7,12-dimethylbenz(a)anthracene (DMBA)-induced tumors in rats. The present studies were designed to evaluate the influence of dietary protein on the ability of rat liver microsomes to mediate DMBA-induced mutagenesis. Female rats (150g) were fed isocaloric diets containing 7.5, 15.0 or 45.0% protein as casein for 2 weeks. All rats were treated with Aroclor (100mg/kg) 5 days before sacrifice. Liver homogenates (S-9) were prepared and evaluated for their influence on the mutagenicity of DMBA (20 g/plate) with Salmonella typhimurium TA98. S-9 fractions from rats fed the 7.5% protein diet produced approximately 100% more DMBA-induced revertants per mg protein than S-9 fractions from rats fed the 15 or 45% protein diets. Pair feeding studies revealed food intake did not account for these differences. The duration of feeding was also found to influence the S-9 activation effects of dietary protein. These results suggest that the Salmonella/microsome mutagenesis assay has potential use as a relatively simple and rapid system to evaluate the influence of dietary protein source and concentration as factors modifying carcinogenesis. (no Refs)

15. EFFECTS OF LEAD ON BENZENE METABOLISM.

Denton JE, Potter GD, Santolucito JA

Environmental Monitoring Systems Lab., Las Vegas, NV

Effects of Lead on Benzene Metabolism. Available from National Technical Information Service, Springfield, VA, as PB82-143231;, 10 pp., 1981.

The possibility that Pb could effect benzene metabolism through inhibition of enzyme synthesis, was examined by studies of the effects of chronic oral Pb treatments on benzene conversion to phenol. Rats were given either distilled deionized water or 0.05, 0.58, 17 or 352 ppm Pb solutions as drinking water. After 6, 9, 12, and 15 wk of treatment, rats from each group were sacrificed and in vitro benzene metabolism by benzene hydroxylase was measured in liver enzyme preparations. After 24 wk, the remaining animals were injected ip with 400 mg/kg benzene and urinary phenol levels measured daily for 4 d. The enzyme activity, studied in vitro, was significantly increased in animals that ingested the 352 ppm solution for 6 wk. Also, Pb levels in all groups of animals were significantly higher in tissues from animals that ingested 352 ppm Pb. Although urinary phenol levels accounted for 30-40% of the ip benzene dose, Pb ingestion had no significant effect on phenol excretion. These results suggested that oral Pb treatments had a significant effect on the enzyme responsible for benzene hydroxylation to phenol. However, unknown factors appear to compensate for these changes in vivo. (Author abstract)

16. CHANGES IN ACTIVITIES OF URIDINE DIPHOSPHATE-GLUCURONYL-TRANSFERASES DURING CHEMICAL HEPATOCARCINOGENESIS.

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Gan; 73(2):239-248 1982

Changes in the activities of hepatic uridine diphosphate-glucuronyltransferases (UDP-GTs) were investigated during the induction of hyperplastic nodules (enzyme-altered foci) by a system consisting of diethylnitrosamine (DEN) followed by N-2-fluorenylacetamide (FAA) and including partial hepatectomy. The activity of the late fetal form of UDP-GT, which was assayed towards o-aminophenol (o-GT activity), was induced rapidly by a single ip injection of DEN (200 mg/kg) or 3-methylcholanthrene (40 mg/kg) or by the continuous administration of FAA (0.02% in diet) alone. The activity further increased with the appearance of the nodules, while the activity of the neonatal form, which was assayed toward phenolphthalein (p-GT activity) and was inducible by phenobarbital, increased only slightly. The increased o-GT activity showed a good correlation with the increased number or area of enzyme-altered foci detected by gamma-glutamyltransferase activity staining, but the p-GT activity did not, though it was significantly increased. In hyperplastic nodules and well differentiated hepatomas induced by DEN (0.1% in drinking water, 3 wk) but isolated long after cessation of DEN, o-GT activity was markedly increased, but p-GT activity was decreased or remained at the level of normal rat liver. These data indicate that the increased o-GT activity may be one of the enzyme markers for preneoplastic hepatic cells. An antioxidant, butylated hydroxyanisole (BHA) (0.75% in diet), markedly elevated the hepatic o-GT activity rapidly after being administered with FAA in the above system, and the induction of the nodules was inhibited. (Author abstract) (32 Refs)

17. PRETREATMENT OF RATS WITH A SINGLE DOSE OF ACETYLAMINOFLUORENE INCREASES THE CAPACITY OF LIVER ENZYMES TO MOVE O6-METHYLGUANINE FROM DNA IN VIVO AND IN VITRO (MEETING ABSTRACT)

Cooper DP, Margison GP, O'Connor PJ

Christie Hospital, Manchester, England

Br J Cancer; 44(2):272 1981

Chronic pretreatment of rats with AAF (acetylaminofluorene) has been shown to enhance the repair of O6-methylguanine (O6-meG) and similar effects have now been obtained using single-dose pretreatments. Male Wistar rats were given AAF up to 20 mg/kg; ip 24 h before a single dose (1 mg/kg, ip) of [14C]-dimethylnitrosamine (DMN). Five h after the DMN challenge there were some variations in the amounts of 7-methylguanine (7-meG) and 3-methyladenine (3-meA) in the liver DNA of control and pretreated groups. However, the 3-meA/7-meG ratio was similar in all cases, while the O6-/7-meG ratio was reduced after 20 mg AAF/kg, suggesting that repair of O6-meG was enhanced. The effect was not specific for DMN-induced damage, as the repair of O6-meG produced in liver by MNU was also enhanced. Incubation of cell-free liver extracts with MNU-methylated DNA in vitro decreased the amount of O6-meG in the acid precipitable DNA. This decrease was protein-dependent, but no free O6-meG base was found in the acid supernatants. Extracts from control rats destroyed 21% of the O6-meG in the substrate, while extracts from animals pretreated with 6.67, 20 or 60 mg AAF/kg destroyed 40, 77 and 90% of the O6-meG respectively. The effects observed in vivo were therefore probably due to an increased production of repair enzyme. AAF pretreatment did not affect 7-meG glycosylase activity in cell-free extracts. There was a 20-fold increase in the incorporation of [3H]-dT into hepatic DNA of rats pretreated with 20 mg AAF/kg, while lower doses had no effect. The enhancement of O6-meG repair could therefore be related either to cell proliferation as a result of the hepatotoxicity of AAF or to the induction of repair enzymes in response to sublethal DNA damage. (1 Ref)

18. DISSOCIATION BETWEEN GUANYLATE CYCLASE - INHIBITION AND ANTIPAPILLOMA EFFECT OF RETINOIDS (MEETING ABSTRACT)

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Acta Pharmacol Toxicol [Suppl] (Copenh), 49(3):41 1981

Retinoids (derivates of vit A) has in recent years gained much attention for their marked effects as chemotherapeutic and chemopreventive agents in cancer. The cellular events leading to cell growth and transformation is largely unknown, although cGMP (cyclic guanosine monophosphate) has been implicated as a mediator. The cGMP forming enzyme guanylate cyclase (GC) is known to be activated by different nitrocompounds and most markedly by the carcinogen N-methyl-N'-nitro-N-nitroso-guanidine (MNNG). Since GC was found to be strongly inhibited by retinylacetate, we initiated a study upon the effect of different retinoids on GC-activity in order to find out if any correlation between GC-inhibiting activity and anti-cancer effect existed. Experiments were performed on nitroprusside (NP) stimulated GC from rat liver (37,000xg supernatant). NP stimulation was found to be qualitatively the same as MNNG stimulation. The different retinoids were kindly supplied by F Hoffman La Roche and Co Basel Switzerland, and included both analogues with the vit A core left intact, and aromatic retinoids which has been found to possess very potent antipapilloma effect when tested on mouse in vivo. The effect on GC activity of the different retinoids, as obtained in our experiments, were compared to values for antipapilloma effect compiled from literature. This comparison revealed no clear correlation between GC-inhibition and antipapilloma effect. Thus, GC-inhibiting activity was found for some retinoids which were totally inactive in vivo and, on the contrary, some of the highly potent aromatic retinoids showed no GC-inhibiting activity. It was also difficult to find any resemblance in the molecular formula for different retinoids with GC-inhibiting action, which could explain their effect on the enzyme. (no Refs)

19. DIETARY MODIFICATION OF METABOLISM AND TOXICITY OF CHEMICAL SUBSTANCES - WITH SPECIAL REFERENCE TO CARBOHYDRATE.

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Biochem Pharmacol; 31(6):1005-1011 1982

Rats were fed various test diets only on the day before sacrifice or every day for 3 wk prior to sacrifice in order to assess the effects of protein (casein), fat (a mixture of olive and corn oils) and carbohydrate (sucrose) on the liver mixed-function oxidase activity. The activity was determined by measuring metabolic rates of eight volatile hydrocarbons, ie, benzene, toluene, styrene, chloroform, carbon tetrachloride, 1,2-dichloroethane, 1,1-dichloroethylene, and trichloroethylene. Contrary to the general belief, it was found that carbohydrate, not protein or fat, regulates the metabolism of these hydrocarbons; a diet which was deficient in carbohydrate remarkably enhanced the metabolism irrespective of protein and fat contents in the diet. This conclusion was confirmed by employing two types of diet, one in which the carbohydrate was replaced by an isocaloric amount of protein or fat (thus keeping total calories of each diet constant) and the other in which the carbohydrate content was varied with protein and fat contents fixed (total calories of each diet differed from others according to the carbohydrate content). In accordance with this, dietary carbohydrate intake also exerted a remarkable influence on the hepatoxocity of carbon tetrachloride which needs to be metabolically activated to become cytotoxic; the smaller the intake, the more severe the liver injury. (Author abstract) (28 Refs)

20. RETINOIDS AND INHIBITION OF ORNITHINE DECARBOXYLASE ACTIVITY.

Boutwell RK, Lowe NJ, DeLuca LM, Meyskens FL, McGuire JS, Krueger GG, Goldsmith LA, Kligman AM
McCardle Lab. for Cancer Res., Univ. Wisconsin, Madison, WI, 53706
J Am Acad Dermatol; 6(4,part2):796-800 1982

A model system for production of skin tumors involves a two stage system in which the skin is first exposed to a low dose of a carcinogen (initiator) which has an irreversible effect on epidermal stem cells. The second step involves exposure of skin to agents, which although not carcinogenic, will cause many tumors quickly (promoter). The second agent causes increased somatic cell gene activity, in this case, induction of ornithine decarboxylase (ODC) activity. The tumor promoter, 12-O-tetradecanoylphorbol-13-acetate (TPA) caused a dose dependent induction of ODC activity in mouse skin within 5 hr of a skin application of 1-10 nanomoles. Induction was inhibited by a single application of from 0.034-3.4 nanomoles of retinoic acid (RA) immediately before or after TPA treatment. Of 30 retinoids tested, all trans-RA was most effective. The amount of inhibition of ODC induction was dependent on time of application of RA relative to time of TPA application, and was also correlated with dose and RA structure. A permanently increased level of ODC and its product, putrescine, may be an important component of tumor promotion. (18 Refs)

21. ANTIMUTAGENIC EFFECT OF ISOCYANATES AND RELATED COMPOUNDS IN ESCHERICHIA COLI.

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Gan; 73(2):255-263 1982

Isocyanates and isothiocyanates have been suggested to inactivate enzymes involved in the metabolic activation of chemical carcinogens and the repair of DNA damage. These compounds decrease the mutability of a tester strain of Escherichia coli B under UV irradiation. This paper deals with the antimutagenicity of acylating agents, including isocyanates and isothiocyanates, and some anti-oxidants which are suspected to be anticarcinogenic. The results can be summarized as follows. (1) The antimutagenic effect observed in the present study operates on UV induced mutagenesis but not on x-ray induced mutagenesis (2) This effect operates only on the wild-type strain, H/r30R, but not on Hs30R deficient in the excision repair system. (3) This effect may function through giving the irradiated cells a greater chance to carry out excision repair by prolonging the lag-period before entry into the S-phase. (4) The carbomoylating ability of isocyanates and isothiocyanates may be responsible for the antimutagenicity but other type of reactivities may also be involved. These antimutagens also participate in inactivating enzymes relevant to the metabolic activation of mutagens, resulting in a decrease in the frequency of chemically induced mutagenesis. (Author abstract) (30 Refs)

22. GLUTATHIONE S-TRANSFERASE ACTIVITY: ENHANCEMENT BY COMPOUNDS INHIBITING CHEMICAL CARCINOGENESIS AND BY DIETARY CONSTITUENTS.

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JNCI, 68(3):493-496 1982

Benzyl isothiocyanate, beta-naphthoflavone, coumarin, alpha-angelicalactone, disulfiram, indole-3-carbinol and indole-3-acetonitrile induced increased (GSH) glutathione S-transferase activity in the liver and small intestine in female ICR/Ha mice. All seven compounds are inhibitors of chemical carcinogenesis. In additional work, several dietary constituents increased GSH S-transferase activity. Consumption of diets containing dried powdered preparations of brussel sprouts, cabbage, coffee beans, or tea leaves resulted in increased GSH S-transferase activity. Mice fed an unrefined diet (Purina Rat Chow) had a higher GSH S-transferase activity than those fed a semipurified diet. The results of the present study indicated that the composition of the diet can alter the activity of an important enzyme system having the capacity to detoxify chemical carcinogens. (Author abstract) (28 Refs)

MUTAGENICITY OF ACTIVATED METABOLITES OF CARCINOGENS

23. METABOLIC ACTIVATION OF 3-METHYLCHOLANTHRENE AND BENZO(A)PYRENE TO MUTAGENS IN THE L5178Y/TK ASSAY BY CULTURED EMBRYONIC RODENT CELLS.

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Environ Mutagen; 4(2):109-119 1982

Early passage cultured rodent cells [Crl;COBS CD(SD) BR rats, Crl;COBS CD1 (ICR) BR mice, Ela ENG/SYR hamsters] were used for the activation of 3-methylcholanthrene (3MCA) and benzo(a)pyrene (B(a)P) in the mouse lymphoma L5178Y/TK mutation assay. S9 mix prepared from cells of the same three rodent lines was used for comparison. Both B(a)P and 3MCA were mutagenic when tested with 5% (vol/vol) S9 from all three sources, but were negative in the L5178Y/TK mutation assay without S9. When tested with three different primary mouse embryo cultures B(a)P was negative, but 3MCA was reproducibly positive. Responses were similar with rat embryo cultures. Both B(a)P and 3MCA gave positive results with hamster embryo monolayers; for 3MCA the SHE X and SHE-48 sources were used. Cell contact between the lymphoma cells and the hamster cells was studied with the use inverted microscopes. A mutagenesis assay using intact hamster cells for the metabolic component and L5178Y cells as targets is evidently feasible. (34 Refs)

24. DIFFERENCES IN MURINE PROCARCINOGEN ACTIVATION ENZYMES ARE NOT ACCOMPANIED BY PARALLEL DIFFERENCES IN PROCARCINOGEN-INDUCED SISTER-CHROMATID EXCHANGE.

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Mutat Res; 94(1):143-153 1982

The correlation between sister chromatid exchange (SCE) formation and the induction of hepatic microsomal drug metabolizing enzymes was investigated. p-Chloromethylaniline demethylase activity was measured in regenerating murine liver as an index of responsiveness to induction of drug metabolizing enzymes by administration of phenobarbital (PB). This activity was inducible in both C57Bl/6 and DBA/2 mice. Constitutive enzyme levels were about the same in the two strains, as was the extent of PB induction (6-fold). 3-Methylcholanthrene did not appreciably induced demethylase activity. PB pretreatment did not influence the number of SCEs induced by cyclophosphamide (CP) in liver and bone marrow cells of hepatectomized animals. Liver and bone marrow cells showed very similar SCE formation in response to CP, even through the liver is thought to be the major site of drug metabolism. These results indicate that differences in procarcinogen activation detected by synthetic substrates are not associated with comparable differences in SCE induction. (41 Refs)

25. BIOLOGICALLY ACTIVE AROMATIC AMINES DERIVED FROM CARCINOGENIC POLYCYCLIC AROMATIC HYDROCARBONS: SYNTHESIS AND MUTAGENICITY OF AMINOBENZO(A)PYRENES.

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Mutat Res; 94(1):13-21 1982

The mutagenicities of 6-amino-benzo(a)pyrene (6-NH2-BP), three K-region NH2-BPs (4-amino-benzo(a)pyrene, 11-amino-benzo(a)pyrene and 12-amino-benzo(a)pyrene), and two N,N-diacetyl derivatives, (4-N(acetyl)-2-benzo(a)pyrene and 12-N(acetyl)2-benzo(a)pyrene) were examined in the Ames' tester strains TA 1535, TA 1538, TA98 and TA100 and compared to those of the parent compound, benzo(a)pyrene (BP), and of 2-aminofluorene (AF). In the absence of S9 activation only 6-NH2-BP and high doses of AF induced revertants and only in the tester strains sensitive to frameshift mutagens. In the presence of S9, all the compounds were active in TA100, TA98, and TA1538, but none were mutagenic in TA1535. A dose response was observed for each compound. The N,N-diacetyl derivatives were less mutagenic than their parent amines. At high concentrations, however, there was a decrease in mutagenicity for 4-and 12-NH2-BP which was not found with the diacetyl derivatives. The 4-substituted analogues were clearly the most mutagenic in TA98, with a general order of mutagenicity of 4-NH2-BP greater than 4-N(Ac)2-BP greater than 12-NH2-BP greater than 12-N(Ac)2-BP greater than AF greater than 11-NH2-BP approx = BP greater than 6-NH2-BP. The 4-NH2-BP derivatives were also the most active in TA100. While paraoxon had no effect on the overall activity of 4-NH2-BP in either strain, it did decrease the mutagenicity of 4-N(Ac)2-BP by 75%. These data suggest that arylamines derived from carcinogenic polycyclic aromatic hydrocarbons are activated to potent mutagens primarily through S9-mediated metabolism of the parent amine. (13 Refs)

26. CHARACTERIZATION OF MUTAGENIC URINARY AND BILIARY METABOLITES OF THE HUMAN CARCINOGEN, BENZIDINE (BZ), IN THE RAT (MEETING ABSTRACT)

Lynn RK, Rogers RM, Garvie-Gould C, Milam DF, Scott KF, Ilias AM

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Fed Proc; 41(3):1574 1982

Bacterial mutagenicity studies of the aromatic amine BZ, suggest that the ultimate carcinogenic moiety is produced via metabolic processes. However, the chemical structure of the ultimate carcinogen(s) is currently unknown. Following iv or oral administrations of 14C-BZ, 75% of the radiolabel was excreted in the feces, approx 20% was found in the urine and 5% remained in the animal 05 days after dosing. In bile exteriorized animals up to 70% of the dose was eliminated in the bile. Urinary and biliary metabolites were separated and quantified by high pressure liquid chromatography, and the individual components characterized by mass spectrometry. N-Acetylation, hydroxylation, and glucuronidation were the major pathways leading to the formation of at least 17 radiolabeled urinary and biliary metabolites. Administration of 35S-sodium sulfate prior to BZ produced at least one BZ metabolite which contained 35S. Several of the urinary and biliary metabolites displayed significant mutagenic activity in the Salmonella typhimurium (TA98)-liver S9-beta glucuronidase assay. (no Refs)

27. INDUCTION OF SISTER CHROMATID EXCHANGES AND INHIBITION OF CELLULAR PROLIFERATION IN VITRO. I. CAFFEINE.

Guglielmi GE, Vogt TF, Tice RR
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Environ Mutagen; 4(2):191-200 1982

The ability of caffeine to induce sister-chromatid exchanges (SCEs), and to inhibit cellular proliferation of human lymphocytes in vitro was examined. Caffeine (0.10-4.10 milli(m)M) inhibited cellular proliferation in phytohemagglutinin-stimulated lymphocytes exposed continuously, but not in those receiving an acute 4-hr exposure. Administration of caffeine throughout the culture period induced a significant dose-dependent increase in SCEs, but exposure for 4 hr prior to the DNA synthetic period did not change SCE frequency. Using a linear regression curve derived from least squares analysis of the semilogarithmic plot of rate of SCE induction, the caffeine concentration capable of doubling the control SCE frequency was calculated as 2.4 mM. SCE induction rate in each of three bromodeoxyuridine replication cycles was the same. The mechanism for the results reported here is probably inhibition of DNA synthesis. Inhibition of DNA synthesis by caffeine may involve purine metabolism, transport, and salvage utilization in a direct or an indirect manner. The non-linearity of the SCE dose response curve for caffeine is in contrast to the typical linear graph for other well-known mutagenic/carcinogenic agents, suggesting that there is more than one mechanism of SCE induction. (52 Refs)

28. MUTAGENICITY OF PYROLYSATES FROM GUANIDINE, UREIDE, SECONDARY AMINES AND POLYAMINES FOUND BY THE SALMONELLA/MAMMALIAN-MICROSOME TEST.

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Mutat Res; 101(3):175-187 1982

The mutagenicity of pyrolysates formed from various nitrogenous compounds at 300, 400, 500 and 600 C were assayed in the Salmonella/mammalian-microsome test. Compounds subjected to pyrolysis included guanidine, ureide, and a variety of secondary and polyamines. Pyrolysates from methylguanidine, agmatine, dihydrouracil, dimethylamine, diethylamine, trimethylamine, triethylamine, pyrrolidine, morpholine, sarcosine, piperazine, pipericine, spermine and spermidine were found to be mutagenic. Mutagenicity began to be evident for pyrolysates obtained at temperatures 400-600 C (was highest for 600 C-except for that derived from methyl-guanidine) when S-9 mixture was added. Pyrolysates from morpholine, piperazine, piperidine, spermine and spermidine were toxic for TA98 and TA 100, while those from dimethylamine and diethylamine were toxic for TA98. The pyrolysate from proline had the highest mutagenic activity, on both TA 98 and TA 100, (with metabolic activation). With metabolic activation, the number of revertants of TA 98 induced by the pyrolysates was greater than those of TA 100. Pyrolysates from dimethylamine, diethylamine and pyrrolidine were slightly mutagenic toward TA 100 in the absence of microsomal activation. (44 Refs)

29. PH-SENSITIVE MUTAGENIC ACTIVITY OF OZONE-TREATED 1,2-DIMETHYLHYDRAZINE IN THE SALMONELLA/MICROSOME ASSAY.

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Mutat Res; 94(1):23-29 1982

It has been previously shown that ozonation of 1,2-dimethylhydrazine (DMH) converts this normally inactive compound into a chemical species capable of inducing revertants in the Ames Salmonella typhimurium/microsome assay. It is shown that the mutagenicity of this ozonation-induced product is pH-dependent. The product of ozonation in basic solution was not mutagenic, while the product of ozonation in acidic solution was highly mutagenic. The mutagenic product was inactivated by raising the pH. Mutagenicity of ozonated DMH was detected at concentrations as low as 30 ug/ml at pH 2.5, and 60 ug/ml at pH 7. Toxicity to TA1535 was observed at pH 2.5 at concentrations greater than 600 ug/ml, while DMH ozonated at pH 7 was not toxic at concentrations as great as 3 mg/ml. Spontaneous reversion frequency was not affected by sample pH. These results suggest that ozonation produces a mutagen that is stable in acid but is labile at high pH. That hydrazines may be an exception to the phenomenon of inactivation of chemical carcinogens by ozonation is discussed in light of the use of ozonation in waste water treatment. (20 Refs)

30. MUTAGENICITY OF 4,4'-METHYLENEDIANILINE DERIVATIVES IN THE SALMONELLA HISTIDINE REVERSION ASSAY.

Rao TK, Dorsey GF, Allen BE, Epler JL
Biology Div., Oak Ridge Natl. Lab., Oak Ridge, TN, 37830
Arch Toxicol; 49(3/4):185-190 1982

The compound 4,4'-methylenedianiline and its derivatives were assayed for mutagenicity in the Salmonella/microsomal mutagenicity assay developed by Ames. A specificity to revert strain TA98 suggests a mechanism of frameshift mutagenesis. Liver microsomal preparations (S-9) from rats induced with phenobarbital were most effective for metabolic activation. Alkyl substitution of 4,4'-methylenedianiline did not alter its mutagenic activity; however, substitution of both positions ortho to the amino group eliminated mutagenic activity. Substitution with alkoxy-carbonyl groups eliminated mutagenic activity, whereas halogen substitution (chlorine, fluorine) enhanced the mutagenicity activity. The results presented here show the use of structure-activity studies as predictive tools for the assessment of genotoxic properties of industrial chemicals. (Author abstract) (14 Refs)

31. STUDIES IN THE INDUCTION OF SEX-LINKED RECESSIVE LETHAL MUTATIONS IN DROSOPHILA MELANOGASTER BY NITROHETEROCYCLIC COMPOUNDS.

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Mutat Res; 101(3):209-236 1982

The induction of sex-linked recessive lethals in Drosophila melanogaster by 24 hr nitroheterocyclic compounds was investigated. The adult feeding technique was used in most cases, and injection and larval feeding in others. Of the nitroimidazoles tested, toxicity increased in the order metronidazole, nimorazole, ronidazole, dimetridazole. Among the nitrofurans, only nitrovin, furazolidone, and furaltadone were clearly mutagenic. Nitrofurantoin and niridazole were ambiguous. Nitrofurans were active at lower molar concentrations than were nitroimidazoles. 4-Nitroquinoline oxide was clearly mutagenic when fed to larvae. Drosophila gut flora were shown not to play role in the activation of ZK 26.173 and furazolidine to mutagenic metabolites. Activation of ZK 26.173 was significantly inhibited in Drosophila strains lacking xanthine dehydrogenase and aldehyde oxidase. (72 Refs)

32. MUTAGENICITY, CARCINOGENICITY, AND BIOCHEMICAL ACTIVITY OF ELEVEN NEW 5-NITROFURAN ANALOGS (MEETING ABSTRACT)

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Fed Proc; 41(3):330 1982

New analogs of the bladder carcinogen N-[4-(5-nitro-2-furyl)-2-thiazolyl]formamide, (FANFT), were synthesized and tested for antibacterial activity against Esherichia Coli and Staphylococcus Aureus, and for mutagenicity against Salmonella TA-100 (Ames test). Two compounds were further tested for their ability to induce ornithine decarboxylase (ODC) in the urinary bladder, and for their carcinogenicity in female rats after 46 wks of exposure in diet followed by 20 wks of control feed. The test compounds were: 2-formylamino-4-[2-(5-nitro-2-furyl)vinyl]-1,3-thiazole (I), 2-amino-4-[2-(5-nitro-2-furyl)vinyl]-1,3-thiazole (II), 5-nitro-3,4-diphenyl-2-methyl furoate (III), 5-hydroxylamino-3,4-diphenyl-2-methyl furoate (IV), 5-amino-3,4-diphenyl-2-methyl furoate (V), methyl(2-oxy-3,4-diphenyl-4-cyano)butanoate (VI), methyl(2-oxy-3,4-diphenyl-4-cyano)butenoate (VII), 2,5-dioxy-3,4-diphenyl-3-pyrroline (VIII), 5-(N-acetylamino)-3,4-diphenyl-2-methyl furoate (IX), 5-(N,N-diacetylamino)-3,4-diphenyl-2-methyl furoate (X), and 5-(N-acetylamino)-2-(2-thiazolyl) furane (XI). I and II, the vinyl bridged analogs of FANFT, showed antibacterial activity against both bacteria, were mutagenic to TA-100, and induced urinary bladder ODC; however, they were not carcinogenic in rats. III was antibacterial and mutagenic, and other analogs were neither antibacterial nor mutagenic. (no Refs)

33. MUTAGENICITY OF SOME INDOLES AND RELATED COMPOUNDS IN THE AMES TEST.

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Toxicology; 23(1):1-10 1982

Nineteen indole derivatives and three analogues were studied with the Ames test using strain TA 98. All compounds were tested at 12 different dose levels (3 nanomol to 30 umol/plate). Indole and all monosubstituted indoles were inactive, whereas 2,3-dimethylindole, 2,3,5-trimethylindole, and 2,3,6-trimethylindole were mutagenic; activity of the two mutagenic trimethylindoles was of the same order of magnitude and markedly exceeded that of the mutagenic dimethylindole. Mutagenicity was unaffected by S-9 from Aroclor-induced rats. When the 5-methyl group in 2,3,5-trimethylindole was exchanged for a methoxy group or a nitro group, and when the aromatic ring system of 2,3-dimethylindole was extended to that of 2,3-dimethylbenz(g)indole, mutagenic effects were lost. It was concluded that 2,3-dimethyl substitution of the indole ring is essential for mutagenic activity. (24 Refs)

34. EFFECT OF 4' HALOGEN SUBSTITUTION ON THE MUTAGENICITY OF TRANS-4-ACETAMIDOSTILBENE AND TRANS-4-(N-HYDROXYACETAMIDOSTILBENE IN THE SALMONELLA TYPHIMURIUM TEST SYSTEM.

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J Med Chem; 25(5):593-595 1982

The effect of halogen substituents placed at the 4' position of trans-4-acetamidostilbene (1, AAS) to alter the pattern of biotransformation and thus the mutagenicity of these derivatives was evaluated by comparing the mutagenic effects of 1 on Salmonella typhimurium TA-100 with the corresponding 4'-F (2), 4'-Cl (3), and 4'-Br (4) analogues. The mutagenic properties of trans-4-(N-hydroxyacetamido)stilbene (5) and its 4'-F (6), 4'-Cl (7), and 4'-Br (8) derivatives were also evaluated in this system. Both the amides (1-4) and hydroxamic acids (5-8) required the presence of a metabolic activating system prepared from hamster liver in order to produce a mutagenic effect. All of these compounds were mutagenic to TA-100. Their mutagenic potencies were markedly influenced by the 4'-halogen substituents, the relative mutagenic potencies of the amides being 2 (4'-F) greater than 1 (4'-H), 3 (4'-Cl) greater than 4 (4'-Br), while the hydroxamic acids followed the order of 1 (4'-H) greater than 2 (4'-F) greater than 3 (4'-Cl), 4 (4'-Br). (Author abstract) (17 Refs)

35. COMPARISON OF THE MUTAGENIC POTENCY OF 2-CHLOROETHANOL, 2-BROMOETHANOL, 1,2-EPOXYBUTANE, EPICHLORHYDRIN AND GLYCIDALDEHYDE IN KLEBSIELLA PNEUMONIAE, DROSOPHILA MELANOGASTER AND L5178Y MOUSE LYMPHOMA CELLS.

Knaap AG, Voogd CE, Kramers PG

Natl. Inst. Public Health, P.O. Box 1, 3720 BA Bilthoven, The Netherlands

Mutat Res; 101(3):199-208 1982

The mutagenic activities of a series of chemically related mutagens in the Klebsiella pneumoniae fluctuation test, in the sex-linked recessive lethal test in Drosophila melanogaster, and in the HGPRT forward mutation test in L5178Y mouse lymphoma cells were tested. Compounds investigated included 2-chloroethanol (CE), 2-bromoethanol (BE), 1,2-expoxybutane (EB), epichlorohydrin (ECH), and glycidaldehyde (GA). In the fluctuation test, increased mutation rates were observed at concentrations of 5 and 0.1 milliM (mM) for CE and BE, respectively. Among the epoxides, the lowest effective concentrations were 1.0, 0.1 and 0.01 mM for EB, ECH and GA, respectively. In the sex-linked recessive lethal test, CE and BE were not mutagenic. EB at concentrations of 117 and 233 mM significantly increased mutation frequency. ECH had been shown by others to be mutagenic in this system, a result which was verified here. GA significantly increased mutation frequency at concentrations of 25 mM and higher. In the HGPRT mutation assay, induction of mutations were observed after treatment with EB and ECH, with ECH being the more mutagenic of the two compounds. (23 Refs)

36. COMPARISON OF SISTER CHROMATID EXCHANGE INDUCTION AND KNOWN CARCINOGENIC ACTIVITIES OF VINYL AND ALLYL CARBAMATES.

Cheng M, Conner MK
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Cancer Res; 42(6):2165-2167 1982

In vivo sister chromatid exchange (SCE) induction by vinyl and allyl carbamates was examined in alveolar macrophage, bone marrow, and regenerating liver cells of C57BL/6J x DBA/2J F1 mice. Allyl carbamate was effective in producing increases in SCE frequencies (relative to base-line SCE) over a dose range of 220 umol/kg (approx 2x base line) to 2.2 mmol/kg (3x base line). In general, alveolar macrophage and regenerating liver cells had higher responses, although not significantly, than did bone marrow. Vinyl carbamate produced significant increases in SCE frequencies over a dose range of 10 umol/kg (2x base line) to 75 umol/kg (8 to 10x base line). At the highest dose, SCE frequencies in extrahepatic tissues of hepatectomized mice were significantly higher than in intact mice and, within hepatectomized mice, alveolar macrophage and regenerating liver cell responses were greater than were bone marrow responses. Vinyl carbamate was approx 30x as potent a SCE inducer than we reported previously for ethyl carbamate. To date, our studies of six different carbamate esters have indicated a striking similarity in relative potencies for SCE induction and their known tumorigenic potencies. (Author abstract) (11 Refs)

37. MUTAGENICITY OF DIBROMODULCITOL (DBD, AN ALKYLATING ANTICANCER DRUG) AND ITS MONO- AND BIFUNCTIONAL CONVERSION PRODUCTS STUDIED BY THE SALMONELLA/MICROSOME ASSAY.

Toth K, Sugar J, Somfai-Relle S, Hedegus L
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Carcinogenesis; 3(3):333-336 1982

Dibromodulcitol (DBD) and one of its most important bifunctional transformation products, dianhydrogalactitol (DAG) with similar cytostatic effect, were tested by the Salmonella/microsome assay on strains TA 1535, TA 1538, TA 98 and TA 100 using the plate incorporation technique. Both drugs were direct mutagens in strains TA 1535 and TA 100 and non-mutagenic in other strains. Their mutagenic effect was not influenced by S-9 mix from rat liver. Mutagenicity of DAG was very limited because of its marked toxicity. The other monofunctional alkylating derivatives, ie, 1-bromo-3,6-anhydrodulcitol and 1,2-epoxy-3,6-anhydrodulcitol were highly mutagenic in strains TA 1535 and TA 100 with and without S-9 mix despite having no anticancer effect. Anticancer activity was exerted only by the bifunctional alkylating hexitols (DBD, DAG) which showed moderate mutagenic activity compared to the monofunctional derivatives. No correlation could be established between the mutagenic and anticancer effect of the four structurally related hexitols. Mutagenicity of urine and bile from rats after a single administration of the max tolerated (450 mg/kg) dose of DBD was also examined, and the hexitol components of the same urine sample were identified by the DBD and its mutagenic transformation products were excreted in urine and not through the bile. The mutagenic effect of DBD observed cannot be attributed exclusively to DBD itself, because the parent molecule, like other alkylating agents, easily undergoes spontaneous decomposition under in vitro and in vivo conditions to release both bi- and monofunctional alkylating solvolysis products and these highly reactive derivatives may play a role in this effect. No significant difference in the relative mutagenicity was detected between DBD and cyclophosphamide, used as a reference substance. (Author abstract) (38 Refs)

38. THE STUDY ON THE MUTAGENIC ACTIVITY OF URINE FROM THE PATIENTS RECEIVING ANTI-CANCER DRUGS.

Pak K, Miyakawa M, Yoshida O
Dept. Urology, Shiga Univ. Medical Science, Japan
Hinyokika Kiyo; 27(12):1481-1495 1981

Mutagenic activity of urine from 43 patients with urogenital cancer was tested in the Salmonella typhimurium TA98 and TA100. Ninety-four urine samples were divided into four groups: Group 1, from patients receiving no drugs; Group 2 from patients receiving some drugs except for anti-cancer drugs; Group 3, from patients receiving single anti-cancer drug; Group 4, from patients receiving two anti-cancer drugs. A 24-hr urine was collected for Groups 1 and 2, and a urine from the time of administration to the next early morning was collected for Groups 3 and 4. No concentrates of Group 1 were mutagenic to either strain TA98 or TA100. No concentrates of Group 2 were mutagenic to either strain TA98 or TA100. Eight urine concentrates of Group 3 were mutagenic. The urine concentrate obtained after administration of cyclophosphamide was mutagenic to the strain TA100. Four concentrates from patients receiving adriamycin were mutagenic to the strain TA98 and/or TA100 and two urine concentrates were mutagenic to both strain TA98 and TA100. Two concentrates from patients receiving cis-diamminedichloride platinum were mutagenic to the strain TA100. Four urine concentrates of Group 4 were mutagenic. Both concentrates from the patients receiving adriamycin and 5-fluorouracil were mutagenic to the strain TA98. One urine concentrate from the patients receiving mitomycin C and cytosine arabinoside was mutagenic to the strain TA98. The concentrate from the patient receiving vincristine and actinomycin D was mutagenic to the strain TA98. Our results suggest that urinary metabolites of some anti-cancer drugs might act as an initiator on the urothelium. Although at the present time the detection of mutagenic activity in the urine does not necessarily predict carcinogenesis of the urothelium, the physician who uses anti-cancer drugs should be aware of delayed sequelae on the urinary tract. (77 Refs) (In JPN)

39. MICROBIOLOGICALLY-MEDIATED MUTAGENIC ACTIVITY OF CRUDE OIL.

Cummings BA, Gordon RC
Dept. Microbiology, Colorado State Univ., Fort Collins, CO
Microbiologically-mediated Mutagenic Activity of Crude Oil. Available from National Technical Information Service, Springfield, VA, as PB82-105131:, 302 pp., 1981.

Crude oil was incubated with raw and sterile river water samples and assayed for mutagenic activity by the Ames test to determine the ability of naturally-occurring freshwater microorganisms to form mutagenic biodegradation products from crude oil. River water samples supplemented with inorganic salts were incubated with one percent crude oil in Erlenmeyer flasks for 1-6 wk and 4 and 20 C with shaking. Replicate flasks were extracted at various time intervals with 1,1,2-trichloro-1,2,2-trifluoroethane, the solvent evaporated and the residues taken up in dimethyl sulfoxide for mutagenicity testing. The extracts were assayed for mutagenic activity by the plate incorporation method of the Ames test with Salmonella tester strains TA 100, TA 1535, TA 1537, TA 1538 and TA 98.

Mammalian liver microsomes were not used in the mutagenicity test system as the oil-degrading microorganisms constituted the enzyme activation system in this study. Preliminary studies in Colorado with lagoon water and Black Hollow, Colorado crude oil showed that frameshift mutagens were produced during microbial degradation of the oil. Studies in Alaska with Chena River water and Prudhoe Bay, Alaska crude oil showed that both frameshift and base-pair substitution mutagens were present in the oil after microbial degradation. Mutagenic activity was not detected in either of the crude oils tested prior to incubation. The presence of mutagenic products may be related to the presence of mutagenic products in microbiologically-degraded crude oil. (Author abstract)

40. RELATIONSHIP BETWEEN THE YIELD OF SISTER CHROMATID EXCHANGES AND CHEMICAL STRUCTURE OF THE MUTAGEN.

Seleznева TG, Shatalina IG, Chebotarev AN
Inst. Medical Genetics, Moscow, USSR
Genetika; 18(2):269-274 1982

The relationship between the yield of sister chromatid exchanges (SCE) and the chemical structure of the mutagen was studied in cultured chinese hamster cells. The cells were incubated with 12 different alkylating agents. All mutagens were found to produce a dose-dependent increase of the yield of SCE. The highest incidence of SCE was observed after incubation with benzoquinone derivatives. (13 Refs) (In RUS)

BINDING OF CARCINOGENS AND THEIR METABOLITES TO MACROMOLECULES

41. PHYSICAL BINDING OF DIOL-EPOXIDE DERIVATIVES OF THE CARCINOGEN BENZO(A)PYRENE TO DNA (MEETING ABSTRACT)

MacLeod MC, Selkirk JK
Biology Division, Oak Ridge National Laboratory, Oak Ridge, TN, 37830
Fed Proc; 41(3):685 1982

Two metabolically-formed, diol-epoxide derivatives of the strong carcinogen benzo(a)pyrene [B(a)P], 7,8-dihydroxy-9,10-oxy-7,8,9,10-tetrahydro benzo(a)pyrene (BPDE) and 9,10-dihydroxy-7,8-oxy-7,8, 9,10-tetrahydro benzo(a)pyrene (reverse-BPDE), have been implicated in covalent binding to nuclear proteins in hamster embryo cells treated for 24 hr with B(a)P. However, only BPDE binds to DNA in treated cells. We have used the characteristic bathochromic shift in the absorbance spectra of polycyclic aromatic hydrocarbon DNA intercalation complexes to probe the in vitro physical interactions of BPDE and reverse BPDE with purified DNA. Both diol epoxides form intercalation complexes with similar association constants and intercalation is blocked by low concentrations of Mg++. In addition, the rate of hydrolysis of BPDE and to a lesser extent of reverse BPDE, is enhanced by DNA. This enhancement of hydrolysis is blocked by low concentrations of Mg++ suggesting the involvement of intercalation complexes in the mechanism of enhanced hydrolysis. Thus, the apparent lack of covalent binding of reverse-BPDE to DNA in cell cultures is not due to an inherent inability to physically interact with DNA. (no Refs)

42. NONCOVALENT BINDING OF 7BETA,8ALPHA-DIHYDROXY-9ALPHA,10ALPHA EPOXYTETRAHYDROBENZO[A]PYRENE TO DEOXYRIBONUCLEIC ACID AND ITS CATALYTIC EFFECT ON THE HYDROLYSIS OF THE DIOL EPOXIDE TO TETROL.

Geacintov NE, Yoshida H, Ibanez V, Harvey RG
Chemistry Dept., New York Univ., New York, NY, 10003
Biochemistry; 21(8):1864-1869 1982

In the presence of native DNA the hydrolysis of benzo[a]pyrene-7,8-diol 9,10-epoxide (BPDE) to tetrols (BPT) is markedly accelerated (by a factor of up to approx 80 at 25 C, pH 7.0, in 5 mM sodium cacodylate buffer solution). When stopped-flow kinetic techniques are utilized, it is shown that the pseudo-first-order hydrolysis rate constant KH is smaller by a factor of approx 3 in the presence of equivalent concentrations of denatured DNA, by a factor of 8-25 in the presence of nucleotides, and by a factor of 35-45 in the presence of nucleosides (depending on the nucleotide or nucleoside). In the presence of native DNA, KH increases with increasing DNA concentration and reaches a limiting value of KH = 0.684 ± 0.04 s-1 at DNA concentrations in excess of approx 5 x 10(-4) M (expressed in concentration of nucleotides). A kinetic model based on (1) rapid formation of a noncovalent BPDE-DNA complex followed by (2) slower hydrolysis of BPDE to BPT at these binding sites is consistent with the experimental data. It is shown furthermore that the DNA concentration dependence of KH and of noncovalent intercalative binding of BPDE to DNA is similar and that addition of magnesium ions (which is known to reduce intercalative binding of planar aromatic molecules to DNA) also reduces KH. These results suggest, but do not necessarily prove, that the DNA binding sites at which the hydrolysis of BPDE (to BPT) is catalyzed are intercalative in nature. (Author abstract) (36 Refs)

43. SPECTROSCOPIC CHARACTERIZATIONS AND COMPARISONS OF THE STRUCTURES OF THE COVALENT ADDUCTS DERIVED FROM THE REACTIONS OF 7,8-DIHYDROXY-7,8,9,10-TETRAHYDROBENZO[A]PYRENE-9,10 OXIDE, AND THE 9,10-EPOXIDES OF 7,8,9,10-TETRAHYDROBENZO[A]PYRENE AND 9,10,11,12-TETRAHYDROBENZO[E]PYRENE WITH DNA.

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Carcinogenesis; 3(3):247-253 1982

The conformation of covalent adducts derived from the reactions of racemic 7beta,8alpha-dihydroxy-9alpha,10-alpha-epoxy-7,8,9,10 tetrahydrobenzo[a] pyrene (BaPDE), 9,10-epoxy-7,8,9,10 tetrahydrobenzo[a]pyrene (BaPE), and 9,10-epoxy-9,10,11,12-tetrahydrobenzo[e]pyrene (BePE) with calf thymus DNA in aqueous buffer solution (25 C, pH 7.0) were investigated and compared by means of absorption, fluorescence and electric linear dichroism techniques. Two types of conformations are recognized. Site I is characterized by a red shift (approx 10 nm) in the absorption max of the pyrene nucleus, a significantly reduced fluorescence yield, and a negative electric linear dichroism signal (DeltaA); this site is presumed to involve a near-parallel (within 25 C) orientation of the planar pyrene residue with the planes of the DNA bases, and a relatively strong interaction between the pi electrons of the nucleic acid bases and the pyrene residue. In Site II, there is only a small red-shift in the absorption max (approx 2 nm), a nonzero fluorescence yield, and a postive DeltaA throughout the absorption region of the pyrene residue; in this conformation the pyrene residue is presumed to lie on the outside of the DNA molecule, possibly in one of the grooves. The BaPDE-DNA complex displays predominantly a Site II-type conformation while the BaPE- and BePE-DNA complexes display both Site I and Site II adducts, with Site I, conformations predominating. The lack of hydroxyl groups in BaPE and BePE lead to a loss in stereospecificity in covalent adduct formation. The 7 and 8 hydroxyl groups in BaPDE appear to reduce the probability of formation of Site I-type of covalent adducts, and appear to be, at least in part, responsible for the enantiomeric stereospecificity in the covalent reaction between BaPDE and DNA. (Author abstract) (25 Refs)

44. THE FORMATION OF BENZO[A]PYRENE - DEOXYRIBONUCLEOSIDE ADDUCTS IN VIVO AND IN VITRO.

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Carcinogenesis; 3(3):267-273 1982

The formation of DNA-bound products from benzo[a]pyrene was studied using metabolic activation systems of widely differing cellular and structural integrity. The nature of the benzo[a]pyrene-metabolite-deoxyribonucleoside adducts formed was markedly dependent on the nature of the activation system used. Systems where cellular integrity is preserved, namely mouse skin in vivo and rat liver hepatocytes and lung explants in vitro, when treated with benzo[a]pyrene, formed deoxyribonucleoside adducts of which the major one co-chromatographed with a bay-region diol epoxide-deoxyguanosine adduct, 10beta-(deoxyguanosin-N2-yl)-7beta,8alpha,9alpha-trihydroxy-7,8,9, 10-tetrahydrobenzo[a]pyrene. In striking contrast, the use of activating systems with disrupted cellular integrity such as rat liver, rat lung and mouse skin microsomal fractions, in the presence of benzo[a]pyrene and exogenous DNA, resulted in the formation of deoxyribonucleoside adducts derived predominantly from either a further metabolite of 9-hydroxybenzo[a]pyrene or (+-)benzo[a]pyrene-4,5-epoxide. The consequences of such results are important when considering the widespread use of subcellular fractions such as microsomes as metabolic activating systems for short-term mutagenicity and carcinogenicity tests. (Author abstract) (41 Refs)

45. DISTRIBUTION OF BENZO(A)PYRENE-DNA ADDUCTS WITHIN MAMMALIAN CHROMATIN (MEETING ABSTRACT)

Jack PL, Brookes P
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Br J Cancer; 44(2):274 1981

The distribution of benzo(a)pyrene (BP)-DNA adducts within mammalian cell chromatin was examined by micrococcal nuclease digestion of nuclei from carcinogen-treated cells. Friend erythroleukemia cells, prelabelled with [14C]-dT (deoxythymidine), were treated with 3H-benzo(a)pyrene-7,8-diol-9,10-epoxide (BPDE) and a nuclear fraction prepared. Micrococcal-nuclease digestion of nuclei, harvested immediately after treatment, indicated a 4-fold enrichment of BP-DNA adducts on the linker region between nucleosome cores. Analysis of DNA, isolated from briefly digested nuclei by agarose gel electrophoresis, indicated that mononucleosomes released early during digestion contained slightly more adducts than total DNA. Treatment of primary mouse embryo cells with BPDE showed a similar enrichment of BP-DNA adducts within the linker region, however treatment of such cells with BP for 72 hr (necessary to allow metabolic activation) showed no such preferential location. This apparent difference between the 2 agents was resolved by showing that post treatment incubation of BPDE-treated cells led to a loss of the preferential linker binding. The time-dependent loss of preferential binding was shown to be independent of DNA replication, since it also occurred when hydroxyurea, an inhibitor of DNA synthesis, was present during post-treatment incubation of the confluent cultures. (no Refs)

46. 7,12-DIMETHYLBENZ[A]ANTHRACENE-DEOXYRIBONUCLEOSIDE ADDUCT FORMATION IN VIVO: EVIDENCE FOR THE FORMATION AND BINDING OF A MONOHYDROXYMETHYL-DMBA METABOLITE TO RAT LIVER DNA.

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Carcinogenesis; 3(3):297-301 1982

The polycyclic aromatic hydrocarbon, 7,12-dimethyl benz[a]anthracene (DMBA) is a potent carcinogen to the female Sprague-Dawley rat, and when administered under conditions that have been shown to produce cancer, results in extensive formation of hydrocarbon-deoxyribonucleoside adducts. Sephadex LH-20 and reverse-phase hplc and spectrofluorometric analysis of these adducts demonstrate that at least one adduct results from the binding of 7,12-dimethylbenz[a]anthracene-1,2,3,4-tetrahydro-3,4 dihydroxy-1,2-oxide. In these experiments, employing ip administration of the hydrocarbon, a second more polar adduct was observed. Evidence is presented that this adduct results from the formation of a monohydroxymethyl-methylbenz[a]anthracene-A-ring-diol epoxide. While both of the monohydroxymethyl-DMBA metabolites have been shown to bind cellular DNA following their administration this is the first evidence of monohydroxymethyl-DMBA-deoxyribonucleoside adducts being formed after the administration of DMBA per se. The evidence suggests that this more polar adduct is a 7-hydroxymethyl-12-methylbenz[a]anthracene deoxyribonucleoside adduct. (Author abstract) (25 Refs)

47. MOLECULAR BIOLOGY OF ENVIRONMENTAL AROMATIC HYDROCARBONS. PROGRESS REPORT, JANUARY 1-JUNE 31, 1981.

Weiss SR

Chicago Univ., Chicago, IL

Molecular Biology of Environmental Aromatic Hydrocarbons. Progress Report, January 1 - June 31, 1981. Available from National Technical Information Service, Springfield, VA, as DE81029033;, 12 pp., 1981.

We have been examining the molecular biology of activated polycyclic aromatic hydrocarbons (PAH) in several different ways, using different biochemical systems. The projects involving these systems are as follows: (I) The binding of benzo(a)pyrene-7,8-dihydrodiol to phage DNA; (II) the binding of PAH-expoxide derivatives to single- and double-stranded 0X174 DNA and its effect on viral DNA infectivity; (III) the fate of benzo(a)pyrene adducts on SV40 DNA in infected monkey kidney cells; (IV) the effects of anti-BPDE on tRNA aminoacyl charging and protein synthesis. (Author abstract)

48. CONFORMATION CHANGE OF DNA INDUCED BY 6-OXYBENZO[A]PYRENE RADICAL.

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Gan; 73(2):308-314 1982

The interaction of 6-oxybenzo[a]pyrene radical with DNA with 50% methanol solution was studied in order to determine whether the radical molecule influences DNA conformation. The mode of the interaction of 6-oxybenzo[a]pyrene radical with DNA differed from that of other benzo[a]pyrene derivatives such as 6-hydroxybenzo[a]pyrene, diol-epoxides, etc. The physical binding of the radical molecule to DNA seemed to be transient. This physical binding is most likely due to adsorption at the external surface of DNA, ie, simply contact in character. It is likely that the local base-pairs are tilted by the contact due to hydrophobic interactions. Furthermore, it is concluded that the covalently bound radical molecule, which is mainly introduced on guanine base, induces a twist of the base plane with respect to other base planes. (Author abstract) (34 Refs)

49. DNA DAMAGE, REPAIR AND DMBA METABOLISM IN HUMAN FETAL CELLS (MEETING ABSTRACT)

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Fed Proc; 41(3):1559 1982

The level of DNA damage, repair and replication following UV irradiation and N-ethyl-N-nitrosourea (ENU) treatment as well as the binding and metabolism of 7,12-dimethylbenz(a)anthracene (DMBA) was quantitated and compared in vitro in cells derived from human fetal brain, dermis, kidney, liver, intestine and lung. Using UDS (unscheduled DNA synthesis) as a measurement of DNA repair, fetal brain, kidney and liver cells exhibited lower (30-60%) levels of UDS than did fetal dermal, lung or intestinal cells treated with UV radiation or ENU. The order for repair of UV induced DNA damage was: dermal greater than lung greater than intestinal greater than kidney greater than liver greater than brain cells. The order for UDS following ENU treatment was: lung greater than dermal greater than intestinal greater than brain greater than liver cells. Intestinal cells metabolized DMBA approximately 30%, while brain cells metabolized only 2.6% of the DMBA. Liver, dermal, lung and kidney, metabolized 5-10% of the DMBA during a 48 hour period. Using HPLC (high pressure liquid chromatography), qualitative as well as quantitative differences in the metabolite profiles were observed in each cell culture. The level of DMBA binding to cellular DNA was of the order: intestinal greater than lung greater than liver greater than dermal greater than kidney cells. These studies provide, important information as to how various human fetal organs metabolize DMBA, repair DNA damage and replicate new DNA following carcinogen exposure. (no Refs)

50. DNA ADDUCT FORMATION IN HUMAN AND RAT PANCREATIC EXPLANTS TREATED WITH N-METHYL-N-NITROSOUREA (MNU) (MEETING ABSTRACT)

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State University of New York, Downstate Medical Center, Brooklyn, NY, 11203
Fed Proc; 41(3):1548 1982

To evaluate the carcinogenic process in an in vitro model of pancreatic carcinogenesis the early effects of carcinogens on pancreatic explants in organ culture were studied. We have reported that adult human pancreatic explants can be transformed in organ culture by treatment with MNU. Since adduct formation of carcinogens with DNA is believed to play a role in carcinogenesis and is a measure of the reactivity of carcinogens with cellular macromolecules we have examined the reaction products of this alkylating agent with DNA under conditions, in organ culture, which cause the transformation of human pancreatic explants. Explants were exposed to 14C-MNU for 2 hours in a chemically defined medium. Total DNA was extracted by a modification of the method of Marmur and the purines analyzed after hydrolysis of the DNA in 0.1 M HCl at 70 degrees for 30 min by chromatography on Sephadex G-10. The analysis of methylated purine bases formed in the DNA of human pancreas indicates the formation of 1-methyladenine (0.0045 bases/1000 parent base), 3-methyladenine (0.0210), 7-methyladenine (0.0093), 7-methylguanine (0.239) and 06-methylguanine (0.024). MNU is approximately 1/10 as active in alkylating DNA of rat pancreatic explants as it is in alkylating DNA of human pancreas. (no Refs)

51. ALKYLATION, PERSISTENCE OF DNA LESIONS, CELL SURVIVAL AND MUTATION IN 4 RODENT TUMOUR CELL LINES AFTER EXPOSURE TO N-METHYL-N-NITROSOUREA (MNU) (MEETING ABSTRACT)

Durrant L, Margison GP, Boyle JM
Christie Hospital, Manchester, England
Br J Cancer; 44(2):272 1981

Dose response curves for colony forming ability were determined following incubation with MNU for 30 min at 37C. The D0 values were 0.7, 0.3, 0.4 and 0.07 mM MNU for Chinese hamster cell lines V79 and V79/79, rat Yoshida sarcoma (YS), and mouse leukemia L1210 cells respectively. Induced mutation frequencies for resistance to 6-thioguanine were 13.8, 16.3 and 17.0x10(-4) per mM MNU for V79, V79/79 and L1210 respectively. The methylated purines O6-methylguanine (O6-meG), N7-methylguanine (N7-meG) and 3-methyladenine (3-meA) were determined on DNA hydrolysates extracted at various times after MNU exposure. There was good correlation between cell survival and total methylated purines for all cell lines except L1210, which showed excessive killing. The half-lives of N7-meG and 3-meA varied among the cell lines, from 15-30 h and 3.6-7.2 h respectively. The half-life of O6-meG was greater than 100 h, 21 hr, 5.7 h and 49.5 h in V79, V79/79, YS and L1210 respectively. Cell-free extracts of YS and L1210 were tested for their ability to destroy O6-meG when incubated with methylated DNA in vitro. The activity from YS was at least twice that from L1210. These results indicate that cell survival is not always related to the level of DNA alkylation, and induced mutation frequency does not correlate with the rate of O6-meG removal in these cell lines. (no Refs)

52. DNA REPAIR AND REPLICATION IN MOUSE AND HUMAN LYMPHOCYTES FOLLOWING TREATMENT WITH DNA DAMAGING AGENTS (MEETING ABSTRACT)

Mhaskar DN, Reuter K, Whisler R, D'Ambrosio SM
Department of Pharmacology, The Ohio State University, Columbus, OH, 43210
Fed Proc; 41(3):1558 1982

The extent of DNA repair and replication was measured and compared in mouse spleen (MS) and human peripheral blood mononuclear cells (HPBMC) following in vivo (MS) and/or in vitro (MS and HPBMC) treatment with N-ethyl-N-nitrosourea (ENU), bleomycin (BLM) and/or ultraviolet radiation (UV). Both ENU and UV induced UDS in MC and HPBMC in culture. The ENU damage induced in MS in vivo appeared to be lost 24 hr post-treatment, since very low levels of UDS were observed compared to 1 hr post-injection. The level of UDS following a combination of ENU and UV were lower in HPBMC (50%) and MS (30%) treated in culture. ENU also inhibited 30% of the scheduled DNA synthesis (SDS) observed in HPBMC. BLM required the presence of the rat liver microsomes activation system for induction of UDS, but not for inhibition of SDS in MS and HPBMC in culture. BLM however did not appear to induce UDS in MS from mice treated in vivo, although it appeared to inhibit (50%) UDS following UV irradiation of MS cells. These data compares the differences and similarities between different types of DNA damaging agents given in vitro and in vivo and in mouse and human lymphocytes. (no Refs)

53. MISMATCH CORRECTION AT O6-METHYLGUANINE RESIDUES IN E. COLI DNA.

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Nature; 296(5860):868-869 1982

Escherichia coli dam mutants, which lack the major DNA adenine methylase and are hypersensitive to base analog mutagens, were found to be sensitive to the DNA methylating agent N-methy-N'-nitro-N-nitrosoguanidine (MNNG), which introduces O6-methylguanine (m6G) into DNA. The sensitivity was not observed using methylating agents which generate only low amounts of m6G. The introduction of either mutL or mutS mutation (second site mutations which are also part of the correction system) into dam strains abolished the sensitivity to MNNG. The results suggest that mismatch correction occurs at m6G residues in DNA. (16 Refs)

54. CHLOROACETALDEHYDE, A VINYL CHLORIDE METABOLITE, INDUCES ERRORS DURING IN VITRO DNA SYNTHESIS (MEETING ABSTRACT)

Hall JA, Saffhill R
Christie Hospital and Holt Radium Institute, Manchester, England
Br J Cancer; 44(2):272 1981

Chloroacetaldehyde (CA), a rearranged metabolic product of the human carcinogen vinyl chloride, has been shown to be mutagenic in certain microbial systems as well as towards mammalian cells. CA has been reacted with the alternating DNA-like polymers poly(dA-dT) and poly(dC-dG) when, as with DNA, etheno-adducts of the adenine and cytosine bases are formed. These treated polymers, when used as templates for Escherichia coli DNA polymerase I, show a decreased ability to direct DNA synthesis. This is accompanied by an increase in the relative levels of non-complementary nucleotides incorporated into the newly synthesized DNA-like material. This increased with the amount of modified base present in the templates used. With the poly(dA-dT) templates one dGMP (guanosine monophosphate) residue was incorporated for every 60 +/- ethenoadenine residues present, while no dCMP (cytidine monophosphate) misincorporation was detected. One misincorporation of dAMP or dTMP (thymidine monophosphate) occurred in the presence of 30 +/- and 80 +/- ethenocytosine residues respectively in the poly(dC-dG) templates. For the modified poly(dC-dG) templates, a nearest-neighbor analysis shows that the majority of the errors were incorporated opposite the cytosine (or modified cytosine) bases. Extensive analyses of the modifications present in the templates indicate that the misincorporations observed are not due to the presence of apurinic sites or to the formation of uracil or xanthine by demination of the cytosine or adenine bases respectively. We conclude that the non-complementary nucleotide incorporations probably arise from the presence of etheno-adducts in the templates used. (no Refs)

ALTERATION OF MIXED FUNCTION OXIDASES BY CARCINOGENS

55. THE INDUCTION OF CYTOCHROME P-448 DEPENDENT BENZO(A)PYRENE HYDROXYLASE IN SACCHAROMYCES CEREVISIAE.

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Biochem Biophys Res Commun; 105(3):1115-1121 1982

A form of cytochrome P450 with maximal absorption at 448 nanometers was induced in Saccharomyces cerevisiae grown in high glucose medium by benzo(a)pyrene (BP). The inability of BP to induce cytochrome P-448 in yeast grown in low glucose medium indicated that conditions similar to high glucose concentration may be required for cytochrome P-448 production. BP metabolism in yeast was also induced by dimethylnitrosamine and phenobarbital. 3-Methylcholanthrene induced a form of the enzyme with a higher affinity for BP. Addition of lanosterol to medium resulted in decreased affinity for BP. (18 Refs)

56. ESTRADIOL EFFECTS OF 2,3,7,8,TETRACHLORODIBENZO-P-DIOXIN (TCDD) INDUCTION OF ARYL HYDROCARBON HYDROXYLASE (AHH) ACTIVITY IN A NEW MOUSE ENDOMETRIAL CELL LINE (MEETING ABSTRACT)

Stols L, Gurka D, Hollenberg P, Iannaccone P
Department of Pathology, Northwestern University Medical School, Chicago, IL, 60611
Proc Am Assoc Cancer Res; 23:908 1982

Preimplantation mouse embryos exposed in vitro to direct acting carcinogens have been shown to have decreased implantation rates and birth rates. If mouse endometrium has the ability to convert procarcinogens to cytotoxic metabolites or mutagens through activation of microsomal enzymes, exposure of a pregnant mouse to indirect acting procarcinogens can effect implantation and normal development of the fetus. We have isolated a mouse endometrial cell population by mild tryptic digestion of the uterine lining, which shows induction of AHH when TCDD is added to culture for 24 hours. The population of endometrial cells are tetraploid and have been maintained in culture. The cells are adherent to plastic as well as glass and contain numerous large refractile, osmophilic non-membrane-limited granules which are PAS positive but negative when stained with Oil Red O and Alcian Blue. The cells were grown in Dulbeccos modified Eagle's medium (DMEM)-10% fetal calf serum (FCS) with and without estradiol at a concentration of 10-8M and 10-8M. In further experiments, media was changed to DMEM-5% FCS (dextran coated charcoal striped) with and without estradiol. Cell number is increased 1.21 fold after 4 days and 1.45 fold after 6 days in the estradiol treated groups. Cell number is increased 1.32 fold after 4 days in the estradiol treated group grown in striped FCS. Inducibility of AHH activity was investigated by growing cells with and without estradiol and then treating with 0.3nM of TCDD for 24 hours. AHH activity was determined by measuring production of hydroxylated benzo(a)pyrene fluorometrically. Cells grown in the presence of estradiol for 4 days show 11.7 fold induction of AHH activity as opposed to 7.8 fold induction in the cells grown without estradiol. (no Refs)

57. INDUCTION OF HEPATIC MICROSOMAL PROPRANOLOL N-DESISOPROPYLASE ACTIVITY BY 3-METHYLCHOLANTHRENE AND SUDAN III.

Fujita S, Uzui T, Suzuki M, Hirasawa M, Mori Y, Naganuma H, Suzuki T
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Biochem Biophys Res Commun; 105(3):1233-1239 1982

The cytochrome P448-dependence of propranolol metabolism was investigated. Propranolol metabolism was induced in Wistar rat liver (measured in microsomes) to three fold control values by 3-methylcholanthrene or sudan III, and 1.5-2 fold by phenobarbital. 7,8-Benzoflavone inhibited propranolol metabolism. It was concluded that N-desisopropylation, one of the major pathways of propranolol metabolism, is predominantly catalyzed by cytochrome P-448, or by one of the structural gene products of the arylhydrocarbon hydroxylase locus. (21 Refs)

58. ALTERATIONS OF BIOELECTRIC POTENTIAL IN PRIMARY HEPATOCELLULAR CARCINOMAS INDUCED BY N-2-FLUORENYLACETAMIDE OR DIETHYLNITROSAMINE.

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Cancer Biochem Biophys; 6(1):1-6 1982

Primary hepatocellular carcinoma(s) induced in rats by N-2-fluorenylacetamide (AAF) or diethylnitrosamine (DEN) were examined for their bioelectric potential (EP). N-2-Fluorenylacetamide-induced PHC differed from age-matched normal livers by a mean of-12.9, which is significant at p less than 0.001. They also differed from non-PHC-bearing surrounding liver by-4.75 mV, significant at p less than 0.05. Diethylnitrosamine-induced PHC differed from normal liver by-13.5 mV and from background liver by-9.95 mV, both significant at p less than 0.001 To determine the contribution of cell division to these differences, regenerating livers were examined. The levels of mixed function oxidases in PHC and in regenerating livers reported in the literature appeared to correlate with the measured EP. We, therefore, studied the effects of chemical inhibitors and an inducer of this enzyme system. The alterations of mixed function oxidase were demonstrated to parallel those of EP. (Author abstract) (35 Refs)

59. CHEMICALS, CANCER, AND CYTOCHROME P-450.

Alexander LS, Goff HM
Univ. Iowa, Iowa City, IA, 52242
J Chem Educ; 59(3):179-182 1982

Cytochrome P450 (P450) and related monooxygenases mediate a variety of complex chemical reactions, including the processing of many foreign chemical substances in the circulation. Nearly all putative carcinogens (except for the nitrosamides and a few alkylating agents) require enzymatic activation before they can induce neoplastic transformation of normal cells. The ultimate carcinogen is an electrophile which covalently binds to DNA, RNA, protein chains, and/or other molecules of importance to cellular reproduction. P450 is often involved in the involved in the metabolic activation of carcinogens. Available evidence on the role of P450 in detoxification and carcinogen activation, its hypothetical reaction cycle with substrates, and the important chemical models used in delineate its active site structure are discussed. (32 Refs)

60. TRANSFORMATION BY ETHIONINE AND S-ADENOSYLETHIONINE OF RAT LIVER EPITHELIAL CELLS IN CULTURE (MEETING ABSTRACT)

Wilson MJ, Brown JD, Poirier LA
National Cancer Institute, Frederick Cancer Research Facility, Frederick, MD, 21701
Fed Proc; 41(3):281 1982

A normal line of rat liver epithelial cells was grown in Williams' Medium D in the presence and absence of the hepatocarcinogen DL-ethionine. The treated cells were exposed for 12 weeks to 2 levels of ethionine, 5.0 and 7.5 mM. The cultures were then maintained in carcinogen-free medium for an additional 31 weeks. At 4 week intervals throughout the experiment the cells were tested for transformation by: 1) carcinoma production following subcutaneous injection of cells into syngeneic hosts and 2) growth in soft agar. Twenty-one weeks after cessation of treatment, growth in soft agar was observed in cultures treated with both levels of ethionine, and tumors were produced in animals injected of ethionine, and tumors were produced in animals injected with cells treated with 7.5 mM ethionine. Control cultures remained untransformed throughout the experiment. The experiment was repeated using medium in which methionine was replaced by homocysteine. Ethionine was more toxic under these growth conditions; therefore, levels of 0.2 and 0.375 mM L-ethionine were used. In the same study cells were also treated with 0.065 and 0.2 mM L-S-adenosylethionine. Both compounds resulted in transformation of the hepatocytes 8 weeks after cessation of treatment. The results indicate that ethionine transforms hepatocytes in culture and that S-adenosylethionine may be a proximal carcinogenic metabolite of ethionine. (no Refs)

61. INDUCTION OF HEPATIC MIXED FUNCTION OXIDASE ACTIVITY IN TROUT (SALVELINUS FONTINALIS) BY AROCLOR 1254 AND AROMATIC HYDROCARBON PCB REPLACEMENTS.

Addison RF, Zinck ME, Willis DE, Wrench JJ
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Toxicol Appl Pharmacol; 63(2):166-172 1982

The effects of feeding 30 and 100 ug/g body wt of the polychlorinated biphenyl (PCB) mixture Aroclor 1254 and three commercial preparations of PCB replacements, based on phenylxylylethanes and diisopropylnaphthalenes, on the hepatic mixed function oxidase (MFO) system of trout were investigated. Examination of a number of indices of MFO induction, eg cytochrome P-450, benzphetamine N-demethylase, ethoxyresorufin- and ethoxycoumarin O-deethylases, indicated that the PCB replacements may exert some sublethal effects, although not to the extent of Aroclor 1254. The PCB replacements were accumulated and deposited in the fillets about one fifth as efficiently as Aroclor 1254. (24 Refs)

ALTERATION OF OTHER CARCINOGEN-METABOLIZING ENZYMES BY CARCINOGENS

62. INFLUENCE OF 3-METHYLCHOLANTHRENE ON LIVER NUCLEOLAR AND NUCLEOPLASMIC ACTIVITIES OF PROTEIN KINASES AND RNA POLYMERASES.

Kleeberg U, Szeberenyi J, Juhasz P, Tigyi A, Klinger W
Inst. Pharmacology and Toxicology, Friedrich-Schiller Univ., Jena, E. Germany
Biochem Pharmacol; 31(6):1063-1067 1982

The experiments were designed to investigate some details of the action of 3-methylcholanthrene (3-MC) on the regulation of transcription. After a single intraperitoneal dose of 3-MC a significant increase in the activities of both nucleolar and nucleoplasmic protein kinases in hepatic cells of young rats was found. The maximal stimulation took place 24 hr after the administration of 3-MC and the extent of activation was much greater in the nucleolar fraction. There is a significant elevation of the activities of both functional forms, free and template-engaged, of RNA polymerase A 24 hr after a single injection of 3-MC. Free and engaged forms of extranucleolar RNA polymerase B show a different behavior: after 24 hr of 3-MC administration the engaged form is markedly enhanced while the activity of the free enzyme shows a significant decrease. The more moderate increase in total RNA polymerase B activity is obviously preceded by a transfer of the enzyme from 'free' to 'engaged' form. Since the enhancement of protein kinase activities was accompanied by the stimulation of nuclear RNA polymerases we suggest that both kinds of enzymes are involved in an epigenetic mechanism of the inducing action of 3-MC on cytochrome P1-450. (Author abstract) (47 Refs)

63. DIFFERENTIAL INDUCTION OF RAT LIVER MICROSOMAL UDP-GLUCURONOSYLTRANSFERASE ACTIVITIES BY VARIOUS INDUCING AGENTS.

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(c/o Bock) Dept. Pharmacology and Toxicology, Univ. Gottingen, Kreuzbergring 57, W. Germany
Biochem Pharmacol; 31(6):907-913 1982

The selectivity of various inducers of UDP-glucuronosyltransferase was investigated in rat liver microsomes and compared with their effect on monooxygenase reactions. (1) Similar to 3-methylcholanthrene, beta-naphthoflavone selectively stimulated the glucuronidation of 1-naphthol and 4-methylumbelliferone (GT1 substrates). (2) In contrast, DDT preferentially enhanced the glucuronidation of morphine, 4-hydroxybiphenyl (GT2 substrates) and bilirubin, similar to phenobarbital. (3) Clofibric acid and bezafibrate selectively enhanced bilirubin glucuronidation without affecting GT1 and GT2 reactions. (4) Similar to ethoxyquin and Aroclor 1254, trans-stilbene oxide enhanced both GT1 and GT2 activities but not bilirubin glucuronidation. (5) In contrast to 3-methylcholanthrene-type inducers which induce both cytochrome P-450MC and GT1, probably through a common receptor protein, ethoxyquin and trans-stilbene oxide markedly induced GT1 reactions without affecting benzo[a]pyrene monooxygenase. (Author abstract) (61 Refs)

64. ADAPTATION TO ALKYLATION RESISTANCE INVOLVES THE INDUCTION OF A DNA GLYCOSYLASE.

Evensen G, Seeberg E
Inst. General Genetics, Univ. Oslo, Blindern, Oslo 3, Norway
Nature; 296(5859):773-775 1982

The possibility of two pathways for repair of 3-methyladenine residues in Escherichia coli DNA was examined. The first pathway appears to be constitutively expressed and controlled by the gene tag, the second inducible and controlled by ada. Adaptive treatment with N-methyl-N'-nitro-N-nitrosoguanidine (MNNG), used to induce 6-methylguanine DNA methyltransferase, also induced high levels of 3-methyladenine DNA glycosylase activity in the tag mutant (BK2114). This induction was not seen in the tag ada double mutant (BK2106). BK2114 additionally regained its ability to reactivate alkylated phages. These results indicate the induction of two separate enzymes for repair of alkylated DNA: 6-methylguanine DNA methyltransferase and 3-methyladenine DNA glycosylase. Both of these enzymes appear under ada control. Since the ada mutation prevents induction of these two separate repair enzymes, the ada gene may be a control gene for the adaptive response. Structural genes for one or both enzymes may be situated elsewhere on the chromosome. Another mutant, alk-1, was found deficient in the induction of TagII but proficient in induction of the methyltransferase. 6-Methylguanine DNA methyltransferase is thought responsible for mutagenic adaptation, while ada+-dependent inducible glycosylase may be responsible for killing adaptation, because DNA polymerase I is required to complete repair of the apurinic site formed by glycosylase action. (14 Refs)

65. IN VITRO INHIBITION OF DNA METHYLASE (DMASE) BY DIRECT CARCINOGENS AND THE PROTECTIVE ABILITY OF THIOL REDUCING AGENTS (MEETING ABSTRACT)

Chan JY, Ruchirawat M, Lapeyre JN, Becker FF
M. D. Anderson Hospital and Tumor Institute, Houston, TX, 77030
Fed Proc; 41(3):685 1982

The role of DNA methylation during carcinogenesis is unknown although DNA from carcinogen-treated rat liver is hypomethylated. To determine if carcinogens directly affect DMase, the direct-acting carcinogens acetoxyacetylaminofluorene (AcAAF) and methylnitrosourea (MNU) were tested in vitro on DMase activity from rat liver. Fifty percent inhibition of DMase activity was achieved with 4.3 mM AcAAF and 47 mM MNU. The sensitivity of DMase towards direct carcinogens was similar to that for DNA polymerase-alpha, while DNA polymerase-beta, the putative repair enzyme, was highly resistant to carcinogen damage. When various thiol reducing agents were tested for their ability to protect DMase from carcinogen damage, differential protective ability was observed. Dithiothreitol, beta-mercaptoethanol and reduced glutathione were effective in protecting DMase from AcAAF damage while the effects of cysteine and ergothioneine were small. At 10 mM of these agents, the percent of DMase activity recovered after interaction with 6.7 mM of AcAAF was 94,86,78,34 and 12, respectively. These effects may have some bearing on the DNA hypomethylation observed in vivo, suggesting that the carcinogens tested may achieve their inhibitory effect by affecting crucial thiol(s). These data also suggest that various intracellular thiols may play an important role in protecting DNA modifying enzymes from carcinogen damage. (no Refs)

66. INDUCTION OF A DNA GLYCOSYLASE FOR N-METHYLATED PURINES IS PART OF THE ADAPTIVE RESPONSE TO ALKYLATING AGENTS.

Karran P, Hjelmgren T, Lindahl T
Imperial Cancer Res. Fund, Mill Hill Lab., Burtonhole Lane, London MW7 1AD, England
Nature; 296(5859):770-773 1982

Adaptation to repetitive DNA alkylation was investigated in Escherichia coli. Only 3-methyladenine DNA glycosylase II, 3-methylguanine DNA glycosylase and 7-methylguanine DNA glycosylase activities were induced during adaptation by N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) treatment. These inducible enzyme activities may be associated with a single enzyme, as the relative levels of induction of the three activities were similar. Separation of these activities was not effected by a variety of chromatographic procedures (diethylaminoethanol-cellulose, Sephadex gel chromatography, DNA-cellulose). 3-Methylguanine was removed slowly in unadapted cells, with 50% remaining in DNA 30 min after treatment with MNNG; in adapted cells, however, about 50% was removed immediately during exposure to mutagen, and by 30 min no residual 3-methylguanine was detected. 3-Methyladenine remained in DNA in both cases. 7-Methyladenine and 1-methyladenine were inefficiently removed in adapted and unadapted cells. These results indicate that 3-methylguanine is responsible for a major part of the cytotoxic effect of methylating agents. (25 Refs)

67. ALTERATIONS IN UREA METABOLISM ASSOCIATED WITH CARCINOGEN ADMINISTRATION (MEETING ABSTRACT)

Jeevanandam M, Brennan MF, Deschner EE
Sloan-Kettering Cancer Center, New York, NY, 10021
Fed Proc; 41(3):280 1982

In an effort to design more efficacious nutritional support, increasing emphasis is being placed upon the metabolic derangements of the cancer bearing host. The breakdown rate of urea was determined in control and following administration of carcinogen to female CF1 mice, fed ad libitum. Two control groups, one (C) 8 wk old, 24.0 g and another age-matched (AMC) 35 wk old, 32.3 g animals were studied. Five wk old mice received 6 weekly injections of methylazoxymethanol acetate. They (CA, 33.0 g) were studied 24 week after the last injection. Each mouse was given intraperitoneally 0.4 uCi 14C-urea in saline. Urine and expired CO2 were analyzed. The increased recovery of 14C in the expired air and in the non-urea constituent of urine in the CA group suggest that the enhanced breakdown of urea was related to the carcinogen administration. The demand for the precursor carbamylphosphate for pyrimidine synthesis may partly be met by the increased breakdown of urea in carcinogen treated mice. (no Refs)

68. DIFFERENCES IN INTRACELLULAR RETENTION OF L-AZASERINE CORRELATE WITH GAMMA-GLUTAMYL TRANSPEPTIDASE ACTIVITY (MEETING ABSTRACT)

Perantoni A, Rice JM, Curphey TJ
National Cancer Institute, Frederick, MD
Fed Proc; 41(3):336 1982

L-Azaserine toxicity and carcinogenicity correlate positively with cellular levels of gamma-glutamyl transpeptidase (GGT). Interest in the basis for this relationship has led to an investigation of the postulated role of GGT in transport of neutral amino acids. Cell lines with difference GGT activities and GGT-deficient cell strains derived by azaserine treatment of TuWi, a human nephroblastoma line high in GGT, were used to test a possible role of GGT in azaserine transport. Uptake of azaserine, a substrate for GGT, does not correlate with cellular GGT activity. Loss of azaserine from cells following its removal from culture medium, however, is correlated with enzyme activity. After exposure to azaserine (0.6 mM, 3 hr) and within 30 min of its removal from medium the hamster lung fibroblast V79, rat liver-derived ARL6T, and TuWi (GGT activities of 0.5, 10, and 46 nmol product/min/mg protein, respectively) retained 3.5, 5.7, and 7.1 nmol azaserine/mg protein. Cell strains of TuWi with GGT activities of 12, 25, 26, and 27 retained azaserine levels of 4.8, 5.5, 6.0 and 6.2 nmol/mg protein, respectively. The same qualitative pattern is maintained as cells continue to lose azaserine with time. Analysis of culture supernatants suggests that the azaserine remains intact. These results are consistent with a role for GGT in the intracellular retention of azaserine and perhaps other neutral amino acids. (no Refs)

69. THE CYTOTOXIC AND MUTAGENIC EFFECTS OF 5-BROMODEOXYURIDINE-PLUS-BLACK-LIGHT TREATMENT IN CULTURED MAMMALIAN CELLS.

Lynn LA, O'Neill JP
(c/o O'Neill) Biology Div., Oak Ridge Natl. Lab., Oak Ridge, TN, 37830
Mutat Res; 94(1):179-187 1982

The cytotoxic and mutagenic effects of bromodeoxyuridine (BrdUrd) plus black light (360 nanometer) on Chinese hamster ovary (CHO) cells were investigated. CHO cells were initially incubated with different concentrations of BrdUrd for 25 hr (conditions known to be mutagenic) prior to exposure to black light. Cultures were incubated with 0, 2, 10 and 50 uM BrdUrd and exposed to black light for 0-300 min. Black light alone showed no cytotoxic or mutagenic effects. With increasing duration of light exposure, an exponential decline in cell survival was observed with each BrdUrd concentration, and the slope of the line increased with the concentration of BrdUrd. Light exposure also resulted in mutation induction with 2 and 10 uM BrdUrd, concentrations which alone were not mutagenic, and in increases above the mutant frequency induced by 50 uM BrdUrd alone. These results indicate that the lack of mutagenicity of BrdUrd concentrations of 10 uM or less is not due to a lack of incorporation into the hypoxanthine-guanine-phosphoribosyl-transferase locus, since subsequent exposure to black light and photolysis of the incorporated BrdUrd can be detected as an increase in the frequency of thioguanine-resistant mutants. This methodology might be used to study specific-locus repair in a manner analogous to the BrdUrd-incorporation method described by Regan et al. (19 Refs)

REVIEWS AND OTHER RELEVANT STUDIES

70. EFFECTS OF COAL-COMBUSTION EFFLUENT ON PULMONARY CARCINOGEN METABOLISMS. QUARTERLY PROGRESS REPORT.

Colby HD
West Virginia Univ., Sch. Medicine, Morgantown, WV
Effects of Coal-Combustion Effluent on Pulmonary Carcinogen Metabolisms. Quarterly Progress Report. Available from National Technical Information Service, Springfield, VA, as DE81023278:, 3 pp., 1981.

This paper summarizes the direct effects of heavy metals in vitro on pulmonary, hepatic, and adrenal mixed function oxidases including those involved in the metabolism of various carcinogens such as benzo(a)pyrene. Apparent enzyme activity decreased as a function of increasing incubation time for the assay. These observations further illustrate the relevance of the preincubation type experiments described in previous reports. Thus, duration of exposure to metals appears to be an important determinant of the effects on microsomal carcinogen metabolism. Since many heavy metals have extremely long half-lives in tissues in vitro, prolonged duration of exposure may contribute significantly to the toxicity of heavy metals. (Author abstract)

71. CULTIVATED MUSHROOM MYCOTOXINS: CARCINOGENESIS AND CHEMISTRY (MEETING ABSTRACT)

Toth B, Ross A
University of Nebraska Medical Center, Omaha, NE, 68105
VI Meeting of the European Association for Cancer Research, October 12-15, 1981, Budapest, Hungary. The European Association for Cancer Research 275 pp., 1981.

Agaricus bisporus, the commonly eaten cultivated mushroom of commerce in the Western Hemisphere, contains beta-N-[gamma-L-(+)-glutamyl]-4 hydroxymethylphenylhydrazine (synonym: agaritine, A), its breakdown product 4-hydroxymethylphenylhydrazine (4-HMPH), and 4-(hydroxymethyl)benzenediazonium ion (4-HMBD), etc. It has also been shown in vitro that 4-HMPH yields to 4-methylphenylhydrazine (4-MPH). Carcinogenesis investigations have been performed with these four chemicals in Swiss mice in groups of 100 animals each. Two chemicals in this series, the hydrochloride form of 4-MPH and the N'-acetyl derivative of 4-HMPH, induced tumors of lungs and blood vessels. In addition, the tetrafluoroborate form of 4-HMBD evoked tumors of the subcutis and skin, while the administration of A resulted in no detectable tumorigenic effect. Analytical chemistry investigations also confirmed the presence of A up to 0.2% in the mushroom samples. Furthermore, 4-HMBD was identified in acidic and neutral aqueous extracts of Agaricus bisporus in amounts up to 0.6 ppm. Biochemical studies carried out here also indicated that 4-HMBD is generated from A by an enzyme system present in Agaricus bisporus acting in situ. Finally, if one of the breakdown pathways of A in the mouse gut proceeds via 4-HMBD, this highly labile product is likely to decompose to 4-hydroxy-benzyl alcohol (4-HBA). In this laboratory small amounts of 4-HBA in mouse gut were detected after feeding A. (no Refs)

72. UPTAKE AND LOCALIZATION OF SELENIUM IN MAMMARY EPITHELIAL CELL LINES (MEETING ABSTRACT)

Medina D, Lane H
Baylor College of Medicine, Houston, TX, 77030
Proc Am Assoc Cancer Res; 23:902 1982

Previous experiments demonstrated that selenium supplementation inhibited both viral-and chemical carcinogen-induced mouse mammary tumorigenesis. In order to understand the basis for selenium-mediated inhibition of mammary tumorigenesis, the uptake and localization of selenium was examined in 3 mammary epithelial cell lines (CL-S1, YN-4 and WAZ-2t), which exhibited different sensitivities to selenium-modulation of cell growth. All three cell lines incorporated 75Se over 24-48 hrs, although the maximum amount incorporated was on the order WAZ-2t, YN-4, CL-S1. Glutathione peroxidase, a selenoenzyme, was present in all 3 cell lines with the same relative order. Labeled selenium localized primarily in the cytosol compartment (59%) and secondarily, in the mitochondrial compartment (21-23%). The half-life of labeled selenium in the cells was 2.6 days. After a cold-chase wash, the labeled selenium turned over to the same extent in the cytosol and mitochondrial compartments. The three cell lines were exposed to 5 x 10-8M, 5 x 10-6M, and 5 x 10-5M selenium and processed for examination by transmission electron microscopy. No effects on cellular organelles and general cellular architecture were seen at 5 x 10-8M selenium. At 5 x 10-6M selenium, YN-4 exhibited a marked electron-dense deposit in virtually all of the mitochondria of the cells. Mitochondria of the cell lines CL-S1 and WAZ-2t were unaffected at this dose. (no Refs)

73. ALTERED TISSUE REACTIVITY AND INTERACTIONS BETWEEN CHEMICALS.

Witschi HP
Oak Ridge Natl. Lab., Oak Ridge, TN
Proceedings of the NRC Workshop on Multichemical Contamination, held in Milan, Italy, April 1981. Available from National Technical Information Service, Springfield, VA, as DE81023189:, 33 pp., 1981.

Interactions between chemicals may modify the biological response if exposure is simultaneous or sequential. Two different situations can be distinguished where interactions are caused by sequential exposure: (1) a first agent acts as an inducer or inhibitor of mixed function oxidases. This alters the response to a second, challenging agent. The nature of the biological response, whether enhanced or abolished, is dictated by the second agent; and (2) a first agent produces slight or possibly undetected or undetectable changes in a tissue. Exposure to a second agent enhances or allows expression of the biological response determined by the first agent. Both types of interactions are characterized by a requirement for a strictly ordered sequence of exposure to two chemicals and by complex dose-effect and time-effect relationships. Detection of such interactions is not likely to occur if exposure is simultaneous or unless specific experimental questions dealing with the nature and modification of the biological response are explored. (Author abstract)

74. MUTAGENESIS ASSAY METHODS.

Casciano DA
Div. Mutagenesis Res., Natl. Center Toxicological Res., FDA, Dept. Health and Human Services, Jefferson, AR, 72079
Food Technol; 36(3):48-50,52 1982

Submammalian, as well as several in vitro and in vivo mammalian mutagenesis assay systems currently being used or developed to detect potential mutagens or carcinogens are described and discussed, with particular regard to advantages and disadvantages of each system. Bacterial systems are most useful as prescreens to detect mutagens capable of inducing point mutations and to identify the type of lesion induced at the molecular level. They are inexpensive, rapid, and easily adapted to inclusion of exogenous metabolic activation systems, but they are not readily amenable to detection of chromosome aberrations and results are difficult to extrapolate to man. Uses, advantages, and disadvantages of in vitro mammalian systems are similar to those of submammalian systems, although the former have the advantage of having a mammalian genome as the target molecule. Use of the intact mammal in mutagenicity/carcinogenicity testing provides the closest approach to metabolic conditions in humans. These include the 'spot' test, micronucleus test, sister chromatid exchange, unscheduled DNA synthesis, dominant lethal, heritable translocation, phenotypic specific locus, and biochemical specific locus. (18 Refs)

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NOTICE OF CURRENT REVIEWS: CARCINOGENESIS

As an additional service to readers of carcinogenesis (CK series) CANCERGRAMS, each issue now provides a bibliography of review articles of interest to carcinogenesis researchers, selected from journals screened for that month's CANCERGRAMS.

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Bishop CS, Dye A
East Tennessee State Univ., Johnson City, TN, 37614
J Environ Health; 44(5):231-235 1982

2. DISEASES CAUSED BY EPOXY RESINS.
Konietzko H, Fischer G
Institut fur Arbeits- und Sozialmedizin, Johannes-Gutenberg-Universitat, Obere Zahlbacher Strasse 67, D-6500 Mainz, W. Germany
Zentralbl Arbeitsmed Arbeitsschutz Proph; 32(3):86-91 1982
In GER

3. NITROSAMINES.
Aigner K
Pneumonologische Abteilung, Krankenhaus der Elisabethinen, Fadingerstr. 1, A-4020 Linz-Donau, Austria
Wien Med Wochenschr; 132(71,Suppl):75-79 1982
In GER

4. EXPERIMENTAL TUMORS OF THE PERIPHERAL NERVOUS SYSTEM.
Beniashvili DS
Cancer Res. Center, Tbilisi, USSR
Eksp Onkol; 4(2):12-19 1982
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5. MUTAGENIC, CARCINOGENIC AND TERATOGENIC EFFECTS OF STYRENE.
Sram RJ, Pohlova H, Topinkova E
Klinika hygieny a epidemiologie, Srobarova 48, 100 42 Prague 10, Czechoslovakia
Prac Lek; 34(2):68-72 1982
In CZE

6. DIETHYLSTILBESTROL: EFFECT OF IN UTERO EXPOSURE.
Burke L
Obstetrics/Gynecology Dept., Harvard Medical Sch., Boston, MA
Curr Probl Obstet Gynecol; 5(2):1-58 1981

7. IN UTERO EXPOSURE TO DIETHYLSTILBESTROL: ADVERSE EFFECTS ON THE REPRODUCTIVE TRACT AND REPRODUCTIVE PERFORMANCE IN MALE AND FEMALE OFFSPRING.
Stillman RJ
Dept. Obstetrics and Gynecology, George Washington Univ. Sch. Medicine and Health Sciences, 2150 Pennsylvania Ave., NW, Washington, DC, 20037
Am J Obstet Gynecol; 142(7):905-921 1982

8. BIOLOGICAL EFFECTS OF MINERAL WOOL.
Petersen R, Ehrhorn H, Mousing K, Sabroe S, Silberschmid M, Venstrup-Nielsen SE
Socialmedicinsk institut, Vesterbro Torv 1-3, DK-8000 Arhus C, Denmark
Ugeskr Laeger; 144(17):971-975 1982
In DAN

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9. NATURALLY OCCURRING FOOD TOXICANTS: PHENOLIC SUBSTANCES OF PLANT ORIGIN COMMON IN FOODS.
Singleton VL
Dept. Viticulture and Enology, Univ. California, Davis, CA
Adv Food Res; 27:149-242 1981

10. MUTAGENS, CARCINOGENS, AND TUMOR PROMOTERS IN OUR DAILY FOOD.
Sugimura T
Natl. Cancer Res. Inst., Tsukiji, Chuo-ku, Tokyo, Japan
Cancer, 49(10):1970-1984 1982

11. THE BIOLOGICAL EFFECTS OF CARRAGEENAN AND OTHER SULFATED POLYSACCHARIDES WITH PARTICULAR ATTENTION TO IMMUNOLOGICAL AND CARCINOGENIC PROPERTIES.
Larsen B
Kraeftforskningsinstituttet, DK-8000 Arhus C, Denmark
Ugeskr Laeger; 144(12):860-863 1982
In DAN

12. VARIATIONS AMONG SPECIES AND CELL TYPES IN THE EFFECTS OF CAFFEINE ON MUTAGEN-INDUCED CYTOTOXICITY AND POSTREPLICATION REPAIR OF DNA.
Sivak A, Rudenko L, Teague LG
Arthur D. Little, Inc., Cambridge, MA, 02140
Environ Mutagen; 4(2):143-162 1982

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13. CANCER IN THAILAND: LESSONS FOR CANCER CONTROL.
Miller DG, Sombooncharoen S
Strang Clinic, Preventive Medicine Inst., 55 East 34th St., New York, NY, 10016
Prev Med; 11(2):232-239 1982

14. MEASUREMENT OF CANCER INCIDENCE IN THE UNITED STATES: SOURCES AND USES OF DATA.
Greenberg ER, Colton T, Bagne C
Norris Cotton Cancer Center, Dartmouth-Hitchcock Medical Center, Hanover, NH, 03755
JNCI; 68(5):743-750 1982

15. STUDIES OF CANCER EPIDEMIOLOGY IN THE UNITED STATES OF AMERICA.
Lapin IuE
Moscow, USSR
Feldsher Akush; (2):55-57 1982
In RUS

16. CURRENT CONCEPTS OF THE ETIOLOGY AND PATHOGENESIS OF LUNG CANCER.
Chaklin AV, Gritsiute LA
No affiliation given
Vopr Onkol; 28(2):3-9 1982
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N. N. Petrov Res. Inst. Oncology, Leningrad, USSR
Vopr Onkol; 28(2):105-113 1982
In RUS

18. PSYCHIATRIC ASPECTS OF CANCER.
Peterson LG, Popkin MK, Hall RC
P.O. Box 20708, 6431 Fannin, Houston, TX, 77025
Psychosomatics; 22(9):774-793 1981

19. PREDICTIVE IDENTIFICATION OF HYPERSUSCEPTIBLE INDIVIDUALS.
Omenn GS
Dept. Environmental Health, Univ. Washington, Seattle, WA, 98195
JOM 24(5):369-374 1982

20. CARCINOGENESIS AND CURRENT HYPOTHESIS ON THE TUMOR-HOST INTERACTIONS.
Neiman IM
No affiliation given
Patol Fiziol Eksp Ter; (2):63-70 1981
In RUS

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Richardson BJ, Waid JS
Marine Science Lab., Ministry for Conservation - Victoria, P.O. Box 114, Queenscliff, Victoria 3225, Australia
Search; 13(1/2):17-25 1982

22. SIGNIFICANCE OF ENVIRONMENTAL FACTORS FOR THE DEVELOPMENT OF LEUKEMIA, MYELOMA AND MALIGNANT LYMPHOMA.
Brandt L
Onkologiska kliniken, Lasarettet, Lund, Sweden
Lakartidningen; 79(15):1490-1492 1982
In SWE

23. ENVIRONMENTAL FACTORS AND MALIGNANT HEMATOLOGICAL DISEASES.
Bjorkholm M
Hemataologsektionen, Danderyds sjukhus, Danderyd, Sweden
Lakartidningen; 79(15):1457-1459 1982
In SWE

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24. REGULATION OF GENE EXPRESSION IN NORMAL AND NEOPLASTIC CELLS. A REVIEW.
Hochhauser SJ, Stein GS, Stein JL
Dept. Biochemistry and Molecular Biology, Univ. Florida Coll. Medicine, Gainesville, FL, 32610
Pathobiol Annu; 11:1-29 1981

25. WHAT ARE ISOZYMES TELLING US ABOUT GENE REGULATION IN CANCER?
Weinhouse S
Fels Res. Inst., Temple Univ. Sch. Medicine, Health Sciences Center, Philadelphia, PA, 19140
JNCI; 68(3):343-349 1982

26. CHANGES IN AMINO ACID AND SUGAR TRANSPORT ACTIVITY ASSOCIATED WITH MALIGNANT TRANSFORMATION.
Nishino H, Inui K
Dept. Biochemistry, Kyoto Prefectural Medical Univ., Kyoto, Japan
Tanpakushitsu Kakusan Koso; 26(7):881-895 1981
In JPN

27. CURRENT VIEWS ON THE NATURE OF MYOEPITHELIAL CELLS AND THEIR ROLE IN THE MORPHOGENESIS OF DYSHORMONAL HYPERPLASIAS AND BREAST TUMORS.
Karelina TV
Central Lab. Pathology, Inst. Human Morphology, Moscow, USSR
Arkh Patol; 44(2):69-73 1982
In RUS

MODIFICATION OF CARCINOGENESIS

28. OVERVIEW: RETINOIDS AND CARCINOGENESIS.
Schramm T, Coutelle R
Zentralinstitut fur Krebsforschung, Akademie der Wissenschaften der DDR, Lindenberger Weg 80, DDR-1115 Berlin-Buch, E. Germany
Arch Geschwulstforsch; 52(4):323-336 1982
In GER

29. RETINOIDS, URINARY BLADDER CARCINOGENESIS, AND CHEMOPREVENTION: A REVIEW AND SYNTHESIS.
Lower GM, Kanarek MS
Dept. Veterinary Science, Coll. Agricultural and Life Sciences, Univ. Wisconsin, 1655 Linden Drive, Madison, WI, 53706
Nutr Cancer; 3(2):109-115 1981

30. THE ANTITUMOR POLYSACCHARIDE LENTINAN: AN OVERVIEW.
Chihara G
Natl. Cancer Res. Inst., Tsukiji, Tokyo, Japan
Excerpta Med Int Congr Ser; 576:1-16 1981

VIRAL AND IMMUNOLOGICAL ASPECTS OF CARCINOGENESIS

31. ENDOGENOUS ONCOGENIC TYPE B VIRUSES IN MICE.
Komarova EA, Kriukova IN
All-Union Cancer Res. Center, Moscow, USSR
Eksp Onkol; 4(2):3-12 1982
In RUS

32. GENETIC INTERACTIONS BETWEEN TUMOR VIRUSES AND HOST CELLS.
Rowe WP
Lab. Viral Diseases, Natl. Inst. Allergy and Infectious Diseases, NIH, Bethesda, MD, 20205
Cancer; 49(10):1958-1962 1982

33. THE PERSISTENCE OF RETROVIRUSES.
Weiss RA
Chester Beatty Res. Inst., Fulham Road, London SW3 6JB, England
Symp Soc Gen Microbiol; 33:267-288 1982

34. HOW DO PAPOVA VIRUSES PERSIST IN THEIR HOSTS?
Griffin BE
Imperial Cancer Res. Fund, Lincoln's Inn Fields, London WC2A 3PX, England
Symp Soc Gen Microbiol; 33:227-247 1982

35. THE EPSTEIN-BARR VIRUS: HISTORICAL, BIOLOGIC, PATHOLOGIC AND ONCOLOGIC CONSIDERATIONS.
Seemayer TA, Oligny LL, Gartner JG
Dept. Pathology, Montreal Children's Hosp., Montreal, Quebec, Canada
Perspect Pediatr Pathol; 6:1-33 1981

36. KAPOSI'S SARCOMA: WHY A 'HOMOSEXUAL DISEASE'?
Groopman JE, Gottlieb MS
Div. Hematology-Oncology, Univ. California at Los Angeles Sch. Medicine, Los Angeles, CA
Hosp Pract; 17(5):64F-64G,64J,64N,64O,64R,64T 1982

METHODOLOGY IN CARCINOGENESIS RESEARCH

37. MAJOR APPROACHES TO THE EXPERIMENTAL STUDY OF LUNG CANCER.
Pliss GB, Turusov VS, Zabezhinskii MA
No affiliation given
Vopr Onkol; 28(2):18-22 1982
In RUS

38. ON THE NECESSITY OF MUTAGENICITY TESTING OF NEW DRUGS.
Bogajewski J, Schoneich J
Zaklad Genetyki Czlowieka, PAN, 60-479 Poznan, Poland
Pol Tyg Lek; 37(2):63-67 1982
In POL

OTHER REVIEWS IN CARCINOGENESIS

39. CANCER - PRINCIPLES AND PRACTICE OF ONCOLOGY.
DeVita VT, Hellman S, Rosenberg SA

NCI, Bethesda, MD
Cancer - Principles and Practice of Oncology. Philadelphia, Lippincott, 1926 pp., 1982.

40. MOVABLE GENETIC ELEMENTS.
Watson JD
Cold Spring Harbor Lab., Box 100, Cold Spring Harbor, NY, 11724
Cold Spring Harbor Symp Quant Biol 45(part 1): 445 pp., 1981.

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MECHANISMS OF CARCINOGENESIS

Activation and Metabolism of Carcinogens

SERIES CK08 No. 82/10

OCTOBER, 1982

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METABOLIC ACTIVATION OF CARCINOGENS

1. S-ADENOSYL-L-METHIONINE IS A CARBON DONOR IN THE CONVERSION OF BENZO(A)PYRENE TO 6-HYDROXYMETHYLBENZO(A)PYRENE BY RAT LIVER S-9.

Flesher JW, Stansbury KH, Sydnor KL
Dept. Pharmacology, Univ. Kentucky Coll. Medicine, Lexington, KY, 40536

Cancer Lett; 16(1):91-94 1982

It is reported that S-adenosylmethionine (SAM) can act as methyl donor in the metabolic conversion of benzo(a)pyrene (BP) to 6-hydroxymethylbenzo(a)pyrene (6-OH-CH3-BP) by rat liver S9 fraction. NADPH, MgCl2 and synthetic 6-OH-CH3-BP and 6-methylbenzo(a)pyrene were added to a reaction mixture containing [methyl-H3]-SAM, BP and rat liver S9. High pressure liquid chromatographic analysis of reaction products indicated that either 6-methylbenzo(a)pyrene was not formed, or if formed, was rapidly converted to 6-OH-CH3-BP, the principle radiolabeled metabolite. Whether this meso-hydroxylalkyl metabolite undergoes further bay region ring oxidation or is converted into a reactive ester of the hydroxy-

HE 20.3173/2:

methyl metabolite to form an ultimate carcinogen remains to be seen. (14 Refs)

2. METABOLISM OF BENZO(A)PYRENE AND BENZO(A)PYRENE 4,5-OXIDE IN RABBIT LUNG.

Bend JR, Smith BR, Ball LM, Plummer JL, Wolf CR, Philpot RM, Devereux TR, Fouts JR
Lab. Pharmacology, Natl. Inst. Environmental Health Sciences, NIH, Research Triangle Park, NC, 27709
Adv Exp Med Biol; 136(partA):541-554 1982

Various investigations trying to elucidate some of the metabolic factors that can contribute to the polycyclic aromatic hydrocarbon (PAH)-mediated toxicity in the rabbit lung are described. The PAH used in the studies included benzo(a)pyrene (BP) and benzo(a)pyrene 4,5-oxide (BPO), and a stable K-region arene oxide metabolite of BP, as substrates. In the rabbit, unlike rodents, only minor changes in the rate of BP turnover occur in lung microsomes treated with either 3-methylcholanthrene or phenobarbital. Both microsomal epoxide hydrolase and cytosolic glutathione transferase activities are much lower in rabbit lung than in liver. The metabolism of BP by purified rabbit pulmonary cytochromes P-450 is discussed. Studies of the metabolism of BPO by perfused rabbit lung are described which indicate that equivalent amounts of arene oxides will cause less damage/toxicity in those organs or cells with higher detoxification activity. Studies with perfused lung and liver indicate that BPO is not reduced in vivo. Metabolism of BP and BPO by cells isolated from rabbit lung is discussed. In a recent study, epoxide-metabolizing activities were measured in isolated, sonicated rabbit pulmonary cell fractions, containing varying proportions of Clara and alveolar Type II cells. When BPO was used as the substrate, specific epoxide hydrolase activity was highest in those fractions which contained the greatest proportion of Clara cells. This result was not unexpected since cytochrome P-450 also is preferentially localized in this cell type. (27 Refs)

3. REGIO- AND STEREOSELECTIVITY OF HEPATIC CYTOCHROME P-450 TOWARD POLYCYCLIC AROMATIC HYDROCARBON SUBSTRATES.

Thakker DR, Levin W, Yagi H, Conney AH, Jerina DM
Lab. Bioorganic Chemistry, Natl. Inst. Arthritis, Metabolism and Digestive Diseases, NIH, Bethesda, MD, 20205
Adv Exp Med Biol; 136(partA):525-539 1982

Some aspects of the regio- and stereoselectivity of hepatic cytochrome P-450 (CP) toward selected polycyclic aromatic hydrocarbons (PAH) substrates are discussed. The compounds include: benzo(a)pyrene [B(a)P], benzo(e)pyrene, phenanthrene (PH), benzo(a)anthracene [BA], chrysene [CH], and dibenzo(a,h)anthracene [DBA]. The following areas are explored: substrate specificity of the CP toward PAH substrates, stereoselectivity in the formation of dihydrodiols, and metabolism of dihydrodiols to diol epoxides. Among conclusions drawn, it is noted that PH is metabolized most efficiently whereas CH and DBA are turned over much more slowly. The cytochrome P-450 system and epoxide hydrolase favor formation of dihydrodiols with R,R configuration. The predominant enantiomers of the dihydrodiols with the bay-region double bond as well as bay-region diol epoxides derived from PH, CH, BA and B(a)P, are superimposable when their bay-regions are aligned. These metabolically favored isomers of the dihydrodiols and bay-region diol epoxides are also the more carcinogenic isomers when derived from carcinogenic PAH. (30 Refs)

4. METABOLISM OF POLYCYCLIC AROMATIC HYDROCARBONS IN PLACENTA.

Juchau MR, Chao ST, Namkung MJ
Dept. Pharmacology, Sch. Medicine, SJ-30, Univ. Washington, Seattle, WA, 98195
Adv Exp Med Biol; 136(partA):555-573 1982

Studies concerning the capacity of placental tissues to biotransform and bioactivate polycyclic aromatic hydrocarbons (PAH) and the placental enzyme systems that catalyze these reactions are reviewed. PAH which undergo enzymically-catalyzed monooxygenation in placental tissues include: benzo(a)pyrene (BaP), 7,12-dimethylbenz(a)anthracene (DMBA), N-2-fluorenylacetamide (FAA), 3-methylcholanthrene (3MC), chrysene, benzo(e)pyrene, dibenz(a,h)anthracene and benz(a)anthracene. For each of these substrates, hydroxylation rates are increased by preexposure of the maternal organism to 3MC, but not to phenobarbital-type inducers. Placental enzymes can catalyze the conversion of at least three of these substrates (DMBA, BaP and FAA) to reactive intermediates. Recent studies indicate that a number of P-450 cytochromes that are not spectrally detectable with current methods are responsible for the limited bioactivation observed. 3MC- and phenobarbital-inducible monooxygenases also catalyze the conversion of estrogens to catechol estrogens in placental tissues of humans and experimental animals. The in vivo significance of these observations remains to be clarified. (52 Refs)

5. STEREOSELECTIVE FORMATION OF BENZ(A)ANTHRACENE (+)-(5S,6R)-OXIDE AND (+)-(8R,9S)-OXIDE BY A HIGHLY PURIFIED AND RECONSTITUTED SYSTEM CONTAINING CYTOCHROME P-450C.

van Bladeren PJ, Armstrong RN, Cobb D, Thakker DR, Ryan DE, Thomas PE, Sharma ND, Boyd DR, Levin W, Jerina DM
Lab. Bioorganic Chemistry, Natl. Inst. Arthritis, Diabetes, and Digestive and Kidney Diseases, NIH, Bethesda, MD, 20205
Biochem Biophys Res Commun; 106(2):602-609 1982

The enantiomeric purity and absolute configurations of the 5,6-and 8,9-oxides formed from benzo(a)anthracene (BA) upon incubation with a highly purified and reconstituted system containing cytochrome P450c were investigated. Exceptionally high stereoselectivity in the metabolism of BA to its 5,6-and 8,9-oxides by the reconstituted system was observed. Opposite stereoheterotopic faces of the hydrocarbon must have been epoxidized in order to form the observed enantiomers, a result predicted by a recent theoretical model of the steric requirements of the catalytic site of cytochrome P450c. Since liver microsomes from 3-methylcholanthrene-treated rats formed almost exclusively the (-)-(8R,9R)-enantiomer of the 8,9-dihydrodiol in other studies, it was presumed that epoxide hydrolase must selectively add water with inversion of configuration at the 9-position of the (+)-(8R,9S)-oxide. Eighty percent of the 5,6-dihydrodiol formed has been previously shown to have the (+)-(5R,6R) configuration and 20% the (-)-(5S,6S) configuration. The present study has established that epoxide hydrolase has a fourfold preference for attack with inversion at the (5S)-carbon relative to the (6R) carbon, since the 5,6-dihydrodiol was formed from pure enantiomers (+)-(5S,6R)-oxide. (26 Refs)

6. THE METABOLIC ACTIVATION OF SOME POLYCYCLIC HYDROCARBONS: THE ROLE OF DIHYDRODIOLS AND DIOL-EPOXIDES.

Sims P

Chester Beatty Res. Inst., Inst. Cancer Res., Royal Cancer Hosp., Fulham Road, London SW3 6JB, Japan

Adv Exp Med Biol; 136(partA):487-[illegible] 1982

The role of dihydrodiols and diol-epoxides as reactive intermediates in the process by which polycyclic aromatic hydrocarbons induce cancer were discussed. The discussion was based on studies on the metabolic activation of three typical polycyclic hydrocarbons, the active carcinogen 7-methlybenz(a)anthracene (7-MBA), and the relatively weak carcinogens benz(a)anthracene (BA) and dibenz(a,c)anthracene (DBA). The metabolic activation of 7-MBA appears to involve one or both isomers of the 'bay region' diol-epoxide, 3,4-dihydrodiol 1,2-oxide. On the other hand, the roles played by the 3,4-dihydrodiol 1,2-oxide and 8,9-dihydrodiol 10,11-oxide in the metabolic activation of BA are not yet clear. Both the 3,4-and 8,9-dihydrodiols are metabolites of BA in mouse skin and both appear to be further metabolized to diol-epoxides. In the metabolism of DBA, the 1,2-and 3,4-dihydrodiols, which might give rise to vicinal diol-epoxides on further metabolism, also exist in quasi-diaxial conformations and thus may not yield these reactive intermediates. Overall, the mechanisms involved in the metabolic activation of DBA are still unclear. (38 Refs)

7. HIGHLY TUMORIGENIC BAY-REGION DIOL EPOXIDES FROM THE WEAK CARCINOGEN BENZO(C)PHENANTHRENE.

Jerina DM, Sayer JM, Yagi H, Croisy-Delcey M, Ittah Y, Thakker DR, Wood AW, Chang RL, Levin CW, Conney AH

Lab. Bioorganic Chemistry, Natl. Inst. Arthritis, Metabolism, and Digestive Diseases, NIH, Bethesda, MD, 20205

Adv Exp Med Biol; 136(partA):501-523 1982

The bay-region theory proposing that diol epoxides of carcinogenic polycyclic aromatic hydrocarbons would have the highest biological activity when they were on angular benzorings and when the epoxide group was part of the bay-region was studied with respect to diol epoxides of benzo(c)phenanthrene (BcP), which has an unusually hindered bay-region. Mutagenicity of BcP derivatives in bacterial and mammalian cells was studied, either for inherent mutagenic activity or activity on metabolic activation. In bacterial tests with metabolic activation, the most active compound was the 3,4-dihydrodiol with the bay-region 1,2-double bond, exhibiting 4-fold more activity than BcP and approx 10-fold more activity than the other dihydrodiols tested. In tumorigenicity studies, the 1,2-and 5,6-dihydrodiols were inactive, while the 3,4-dihydrodiol with a bay-region 1,2-double bond was almost 2x as active as BcP. These results strongly implicate bay-region diol epoxides as ultimate carcinogenic metabolites of BcP. On mouse skin, the diol epoxide-1 and diol epoxide-2 diastereomers had similar tumorigenic activity, which was unexpectedly high; approx 15x more active than benzo(a)anthracene 3,4-diol-1,2-epoxide-2, previously the most active diol epoxide tested on mouse skin. A sound basis for the unusually high biological activity of these diol epoxides is currently not available. Some unique feature of the shape of BcP may account for the remarkable biological activity of its bay-region diol epoxides and the high degree of crowding in the bay-region of BcP may be a contributing factor. (46 Refs)

8. HIGH SKIN TUMOUR INITIATING ACTIVITY OF THE METABOLICALLY DERIVED TRANS-3,4-DIHYDRO-3,4-DIOL OF THE CARCINOGEN 15,16-DIHYDRO-11-METHYLCYCLOPENTA[A]PHENANTHREN-17-ONE.

Coombs MM, Bhatt TS

Chemistry Lab., Imperial Cancer Res. Fund, Lincoln's Inn Fields, London WC2A 3PX, England

Carcinogenesis; 3(4):449-451 1982

Eight main metabolites of the parent carcinogen 15,16-dihydro-11-methylcyclopenta[a]phenanthrene-17-one (I) were assayed for their ability to initiate skin tumors in TO mice after topical application in two-stage experiments with croton oil used as the promoter. All were less active than I with the exception of the trans-3,4-dihydro-3,4-diol which was more than 10x as active. This diol is therefore confirmed as the proximate carcinogen, a conclusion reached previously on different evidence. (Author abstract) (13 Refs)

9. MECHANISM OF ESOPHAGEAL TUMOR INDUCTION IN RATS BY N-NITROSOMETHYLBENZYLAMINE AND ITS RING-METHYLATED ANALOG N-NITROSOMETHYL(4-METHYLBENZYL)AMINE.

Hodgson RM, Schweinsberg F, Wiessler M, Kleihues P

(c/o Kleihues), Pathologisches Institut, Albertstrasse 19, 78 Freiburg, W. Germany

Cancer Res; 42(7):2836-2840 1982

The metabolism of the esophageal carcinogen N-nitrosomethylamine (MBN) and its ring-methylated analog N-nitrosomethyl(4-methylbenzyl)amine (4-MeMBN) was investigated in male Wistar rats. When given in drinking water, both compounds have been shown to induce a high incidence of esophageal carcinomas but, after systemic administration of equimolar doses, 4-MeMBN is considerably less toxic and carcinogenic than in MBN. The data indicate that the lower toxicity and carcinogenicity of 4-MeMBN after systemic administration are due to the rapid formation (mainly in the liver) and excretion via the urine of its benzoic acid derivative. The strong carcinogenic effect of po 4-MeMBN can be explained by direct uptake from the drinking water into the esophageal mucosa. Following a single iv injection of [methylene-14C]MBN and 4-Me[methylene-14C]MBN, no benzylated bases were detectable in rat tissues. This indicates that the bioactivation of these compounds is initiated predominantly by hydroxylation at the methylene bridge leading to a methylating rather than a benzylating intermediate as the ultimate carcinogen. (14 Refs)

10. METABOLISM OF CARCINOGENIC AND NON-CARCINOGENIC N-NITROSO-N-METHYLAMINOPYRIDINES. I. INVESTIGATIONS IN VITRO.

Heydt G, Eisenbrand G, Preussmann R

Inst. Toxicology and Chemotherapy, German Cancer Res. Center, D-6900 Heidelberg, W. Germany

Carcinogenesis; 3(4):445-448 1982

A comparative study of in vitro metabolism of isomeric N-nitroso-N-methylaminopyridines (NMPY) by rat liver microsomes revealed remarkable differences in the respective rates of potentially activating and deactivating processes. N-Nitroso-N-methyl-2-aminopyridine (2-NMPY), a potent carcinogen in rats and a mutagen in the Ames test was demethylated to a much greater extent than its non-carcinogenic and non-mutagenic isomers 3-NMPY and 4-NMPY. In contrast to the findings for 2-NMPY, enzymatic denitrosation and N-oxide forma-

tion play a substantial role in metabolism of 3-NMPY and 4-NMPY. The respective rates of presumed activating to deactivating metabolic processes were found to be approx 1.5 for 3-NMPY, 0.5 for 4-NMPY, but 3 for 2-NMPY at 10 mM substrate concentration. At 1 mM concentration (which is more close to the conditions prevailing in carcinogenicity experiments), however, the respective ratio for 2-NMPY was approx 50. 2-Hydroxypyridine, the hydrolysis product of the putative pyridine-2-diazonium intermediate, generated after oxidative demethylation, was formed in high yields from 2-NMPY. Only traces of 3-hydroxypyridine were formed from 3-NMPY and 4-hydroxypyridine could not be detected at all. Experimental evidence suggests that generation of 2-aminopyridine, which was found in high yields after incubation of 2-NMPY, is explained best by a secondary metabolic process: reductive cleavage of azo coupling products formed by reaction of the pyridine-2-diazonium intermediate with appropriate nucleophiles in the incubation mixture. (Author abstract) (8 Refs)

11. INVESTIGATIONS OF THE BIOACTIVATION OF N-NITROSOPYRROLIDINE IN THE RAT.

Cottrell RC, Lake BG, Phillips JC, Young PJ, Walters DG, Allars AJ, Gangolli SD
British Industrial Biological Res. Assoc., Carshalton, Surrey SM5 4DS, England
Adv Exp Med Biol; 136(partB):1165-1171 1982

Metabolism of N-nitrosopyrrolidine (NPYR) in rat liver is discussed. NPYR appears to competitively inhibit the conversion of N-nitrosodimethylamine (NDMA) to formaldehyde by rat liver 10,000 gravity supernatant preparations. A major difference between NYPR and NDMA was observed in the metabolism to 14CO2 by the isolated perfused liver. While the rate of conversion was sufficiently rapid to account for the rate observed in the intact animal, the rate of degradation of NYPR was consistently much slower in the isolated liver. At least three routes of biodegradation of NYPR occur in the rat. One route involves an initial rearrangement reaction, or apparent rearrangement to yield pyrrolidinone-2-oxime (PDO) which was detected radiolabeled in the urine of rats given a high dose of [2,5-14C]NYPR. A second route involves the generation of 4-hydroxybutanol which may be oxidized to 4-hydroxybutyric acid or its lactone. Both of these oxidation products were identified in rat urine. A third route yields 3-hydroxy-N-nitrosopyrrolidine (HNPYR) and, via further metabolism, to C-1 pool precursors and CO2. Identification of radiolabel in urinary dimethylamine but not in methylamine, together with evidence from 3H/14C labeling experiments, indicates the generation of some C-1 pool precursors. PDO was synthesized and found to be relatively non-toxic to rats and inactive in the Ames system. The route via 4-hydroxybutanol has the potential to be an activating route. HNPYR is a mutagen in the Ames system without metabolic activation by rat liver S9; it appeared to be more active alone than NYPR with S9 activation. (13 Refs)

12. METABOLISM OF N'-NITROSONORNICOTINE BY CULTURED RAT ESOPHAGUS.

Hecht SS, Reiss B, Lin D, Williams GM
Naylor Dana Inst. Disease Prevention, American Health Foundation, Valhalla, NY, 10595
Carcinogenesis; 3(4):453-456 1982

The metabolism of N'-nitrosonornicotine (NNN), an esophageal carcinogen, by organ cultured F-344 rat esophagus was investigated. The major metabolites were separated by hplc and were identified by comparison to standards as 4-hydroxy-1-(3-pyridyl)-1-butanone, 4-hydroxy-4-(3-pyridyl)-1-butanol and 4-oxo-4-(3-pyridyl)butyric acid from 2'-hydroxylation of NNN and 4-hydroxy-4-(3-pyridyl)butyric acid from 5'-hydroxylation of NNN. These results demonstrate that alpha-hydroxylation, which leads to electrophilic diazohydroxides, is the major pathway of metabolism of NNN in cultured F-344 rat esophagus. The extents of formation of the metabolites increased with time and the ratio of products resulting from 2'-hydroxylation to those resulting from 5'-hydroxylation was 4.3 after 1 hr, 3.9 after 6 hr, 3.4 after 24 hr and 3.1 after 48 hr. F-344 rat liver slices from the same animals produced metabolites of NNN with a 2'/5'-hydroxylation ratio of 1.4. The 2'/5'-hydroxylation ratio in cultured Syrian golden hamster esophagus was 0.3. These results, together with those of parallel studies of NNN metabolism in A/J mouse lung and Syrian golden hamster trachea indicate that among these tissues, F-344 rat esophagus has a unique ability to preferentially hydroxylate the 2'-position of NNN. The results suggest that 2'-hydroxylation is the key step in the metabolic activation of NNN in rat esophagus. (Author abstract) (18 Refs)

13. METABOLISM AND TOXICITY OF AFLATOXINS.

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Adv Exp Med Biol; 136(partB):847-863 1982

Recent results and experiments on the toxicity and metabolism of aflatoxins are reviewed. In vitro metabolism of aflatoxin B1 (AFB1), characteristics of the AFB1-2,3-oxide and the dihydrol and hemiacetal of AFB1, AFB1-2,3-oxide formation and animal susceptibility, migration of AFB1-2,3-oxide to target sites, questions concerning the effects of phenobarbital pretreatment in in vivo and in vitro studies, and metabolism and toxicity in primary hepatocyte cultures are discussed. The carcinogenic potency of AFB1 in an animal appears to be due to competing pathways of activation and detoxification in the cells, involving the mixed function oxygenases in the endoplasmic reticulum and nuclear membrane and the reductase, epoxide hydrolase, glutathione transferase, and other enzymes in the cytoplasm. These enzymes appear to be localized intracellularly so that no single in vitro metabolism system is able to simulate the in vivo condition to produce a simple set of metabolic parameters for the prediction of AFB1 toxicity. A battery of in vitro assays may represent a successful approach. (54 Refs)

14. METABOLIC ACTIVATION OF 2-ACETYLAMINOFLUORENE.

Thorgeirsson SS, Wirth PJ, Staiano N, Smith CL
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Adv Exp Med Biol; 136(partB):897-919 1982

Metabolic activation of 2-acetylaminofluorene (2AAF) by rat N-hydroxy-2-acetylaminofluorene (N-OH-AAF) N-O-acyltransferase and N-OH-AAF sulfotransferase and mutagenicity of 2AAF in the Ames mutagenicity test are described. Partially purified rat liver N-O acyltransferase markedly increased mutagenicity of N-OH-AAF in the Salmonella test system. With sulfotransferase, the capacity to activate mutagenesis of N-OH-AAF in this assay decreased with each step of purification. Incubation of partially purified N-O acyltransferase with N-OH-AAF and yeast transfer tRNA results in an approx 15-fold increase in the extent of covalent binding of (9-14C) N-OH-AAF to the tRNA. Similar experiments with partially purified sulfotransferase gave no catalysis of covalent binding beyond that observed with the 105,000 g supernatant fraction, unless 3'-phosphoadenosine-5'-phosphosulfate was added; then a 60-fold increase in covalent binding of N-OH-AAF to tRNA was observed. Both ascorbate and NADPH markedly inhibited the covalent binding. The most recent tests system utilizes isolated hepatocytes together with Salmonella tester strains to measure mutagenicity of 2AAF, 2-aminofluorene, and N-OH-AAF. (36 Refs)

15. TWO BIOLOGICAL REACTIVE INTERMEDIATES IN AMINOAZO-DYE CARCINOGENESIS AND THEIR GLUTATHIONE ADDUCTS.

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Adv Exp Med Biol; 136(partB):1297-1306 1982

Evidence is presented for the existence of two reactive intermediates of N,N-dimethyl-4-aminoazobenzene (DAB) and N,N-methyl-4-aminoazobenzene (MAB) and the role of their glutathione (GSH) adducts in the detoxification of aminoazo-dye carcinogens is discussed. The two intermediates apparently have different roles. N-sulfonoxy-N,N-methyl-4-aminoazobenzene (N-s-MAB), or its analogue N-benzoyloxy-N,N-methyl-4-aminoazobenzene (N-b-MAB), is a strong electrophile, is linked with carcinogenesis and mutagenesis, and forms DNA adducts. It must escape reaction with small molecular nucleophiles within the cell, particularly GSH, and GSH may have some limitations as a detoxifying agent for N-s-MAB. GSH trapped 40x as much N-s-MAB as did the macromolecular nucleophiles, demonstrating that it was much more effective in detoxification than the in vitro results suggested. N-methylol-4-aminoazobenzene (N-m-AB) was important in the detoxification of DAB since its GSH adduct, GS-CH2-AB, accounted for 20% of the total biliary excretion of DAB. Optimal excretion of DAB metabolites should depend on the maintenance of hepatic GSH levels. Depletion of hepatic GSH levels can be partly due to the selective inhibition of the formation and excretion of GS-CH2-AB. N-m-AB can also form adducts with thiols, phenols, and amines in nucleic acids; formation of adducts with macromolecules requires further study. (33 Refs)

16. METABOLIC ACTIVATION OF HYDRAZINES.

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Adv Exp Med Biol; 136(partB):971-981 1982

Studies involving metabolism of hydrazine in vivo in mice and in vitro using liver microsomes and whole blood from mice are summarized. Hydrazine was distributed rapidly to most tissues, with the highest levels appearing in the kidney soon after ip injection. After an acute ip dose, hydrazine was lost rapidly from the blood, followed by a much slower decline over the next several hours; losses in urine increased with time. Within the first 1-2 hr after administration of 15N-hydrazine sulfate to male Swiss-Webster mice, approx 20% of the dose was expired as $^{15}N_2$ gas and by 48 hr another 10-15% was eliminated in this form. Mouse liver microsomes were also able to convert hydrazine to nitrogen in a reaction that required enzyme activity, NADPH, and oxygen. This oxidation reaction was not inhibited by a carbon monoxide/oxygen atmosphere. No significant changes in red cell count, total Hb, methemoglobin, or hematocrit were observed 6 hr after administration of a 1 millimole/kg ip dose of hydrazine sulfate to mice. Approx 70% of a dose of hydrazine has been accounted for in N_2 and urinary excretion. (25 Refs)

17. MICROSOMAL METABOLISM OF ACRYLONITRILE IN LIVER AND BRAIN.

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Adv Exp Med Biol; 136(partB):1229-1238 1982

In vitro studies on the metabolism of acrylonitrile (VCN) to cyanide (CN-) are described and metabolizing enzymes and metabolic pathways are characterized. Hepatic enzymes were used to study the metabolism of VCN. Maximal activity of the microsomal metabolism of VCN was observed upon addition of $MgCl_2$ and NADPH to the incubation mixture. Molecular oxygen was also required as shown by the decreased rate (21% of control) of VCN metabolism under anaerobic conditions. Liver microsomes obtained from phenobarbital or Aroclor 1254-treated rats metabolized VCN at a greater rate than control microsomes. Induction of VCN metabolism was also observed with 3-methylcholanthrene treatment, however the increase was not substantial. Decreasing of the hepatic cytochrome P-450 (P-450) content by treatment with $CoCl_2$ resulted in a parallel decrease in the VCN metabolism rate. Effects of inhibitors of the P-450 mixed function oxidase system were also investigated. Incubation mixtures carried out under 80% CO/20% O_2 resulted in substantial decrease in VCN metabolism. The oxidative metabolism of VCN was proposed to proceed via an epoxide or epoxide hydratase. Addition of 10(-4) or 10(-3) M 1,1,1-trichloropyrene-2,3-oxide (TCPO) in dimethyl sulfoxide decreased CN formation by 26%, while the addition of 10(-2) M TCPO resulted in an 81% decrease. These results were in agreement with the proposed pathway. Results indicate that VCN is metabolized to CN- via the P-450 mixed function oxidase system and that epoxide could be an intermediate product of the oxidative metabolism. (18 Refs)

18. METABOLIC ACTIVATION OF TRIAZENE CYTOSTATICS.

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Adv Exp Med Biol; 136(partB):1285-1296 1982

Metabolic activation of 1-(2,4,6-trichlorophenyl)-3,3-dimethyl-triazene (DIC) and 5-(3,3-dimethyl-1-triazeno)imidazole-4-carboxamide (DTIC) was studied in adult male Sprague-Dawley rats. Following sc administration of DIC, a single urinary metabolite with an intact diazoamino structure was detected. The lability of the metabolite pointed to the conjugation through an O-glycosidic bond between glucuronic acid and an 3N-hydroxymethyl group, introduced by metabolic oxidation of one of the 3N-methyl groups of the triazene side-chain. The final 3N-hydroxymethyl-O-glucuronide structure came from field desorption mass spectrometry which established the molecular ion of the metabolite in agreement with the proposed structure. Thin-layer chromatographic examination of urinary excretion products from rats that had been dosed with DTIC confirmed the presence of both previously identified metabolites 5-aminoimidazole-4-carboxamide and 2-azahypoxanthine. The chromatograms also showed the presence of another metabolite with an intact diazoamino group in the molecule. The metabolite was identified as 5-(3-hydroxymethyl-3-methyl-1-triazeno)imidazole-4 carboxamide. Results indicated that enzymic oxidation of 3N-methyl to 3N-methylol sufficiently increased the solubility of the drug so that conjugation with water-soluble endogenous compound does not occur. The formation of 3N-methylols may be an important contributory factor to the broad spectrum of antineoplastic activity of triazene cytostatics. (15 Refs)

19. METABOLISM OF 2,4-DINITROTOLUENE BY RAT HEPATIC MICROSOMES AND CECAL FLORA.

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Adv Exp Med Biol; 136(partA):431-436 1982

The metabolism of 2,4-dinitrotoluene (2,4-DNT) in hepatic microsomes and in the intestinal flora was investigated. Hepatic microsomes were obtained by preparation of livers from male Fischer 344 rats. Cecal microflora was obtained from male rats. [U-14C] 2,4-DNT was incubated at 100 uM with microsomes in 66 milliMoles tris HCl (pH 7.4) for 1 hr; a NADPH generating system was included. An oxygen scavengering system was included in the incubations with nitrogen. The patterns of metabolites produced by the hepatic microsomes was dependent on the oxygen tensions in the incubations. In contrast to microsomes, cecal microflora did not metabolize 2,4-DNT in an air atmosphere, but the 2,4-DNT was rapidly reduced in anaerobic conditions. Both 2-and 4-nitroso-nitrotoluenes were detected in the cecal flora incubations. Comparison of the metabolism of the DNT by the cecal contents and the hepatic microsomes indicated that the reductive metabolic capacity of the cecal contents on a per g wet wt basis exceeds that of the liver by a factor of 1,000, suggesting that the cecum represents a major site for reductive metabolism of DNT; the 2,4-DNT undergoes reduction at either the 2 or 4 nitro group to a nitroso-nitrotoluene. Reduced metabolites of DNT absorbed from the gut would be substrates for the mixed function oxidase (MFO) enzymes in the liver. Oxidations by the MFO system would lead to highly reactive intermediates in the liver. Thus, the liver and cecal microflora acting in concert may be responsible for the carcinogenic activity of DNT. (7 Refs)

20. METABOLIC ACTIVATION AND DEACTIVATION MECHANISMS OF DI-, TRI-, AND TETRACHLOROETHYLENES.

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Adv Exp Med Biol; 136(partA):659-666 1982

Research on the metabolic transformation of mutagenic and carcinogenic chlorinated ethylenes has produced a general scheme in which epoxides, formed from chlorinated ethylenes by monooxygenases, can undergo subsequent transformation via three routes: (1) alkylating substitution with nucleophilic sites of macromolecules; (2) rearrangement, by intramolecular chlorine migration, to chlorinated aldehydes or acyl chlorides; (3) conjugation with glutathione or cysteine and subsequent metabolic transformation, to mercapturic acid derivatives. It is hypothesized that differences in mutagenic activity or inactivity of chlorinated ethylenes may be explained by differences in reactivity of the epoxides. Recent work on the metabolic activation of 1,1-dichloroethylene, trichloroethylene, and tetrachloroethylene is summarized. These in vitro and in vivo experiments have led to the discovery of a variety of new metabolites and a partial revision of the former concepts of metabolic transformation mechanisms. (17 Refs)

21. METABOLISM OF VINYL HALIDES: IN VITRO STUDIES ON ROLES OF POTENTIAL ACTIVATED METABOLITES.

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Adv Exp Med Biol; 136(partA):685-692 1982

Mixed-function oxidation of toxic and carcinogenic vinyl halides is thought to be responsible for the mutagenesis and irreversible binding of metabolites observed with these compounds. One suggested reactive metabolite is a 2-haloethylene oxide, which in turn may rearrange to a 2-haloacetaldehyde, both compounds reacting with nucleophilic targets. Studies are reported examining the ability of purified enzymes to specifically destroy the postulated reactive intermediates of vinyl chloride and vinyl bromide in rat liver microsomal systems, utilizing irreversible binding of vinyl halide labels to protein and DNA as indices of activation. The results are consistent with the view that, in the liver microsomal system, the 2-haloethylene oxides are the species predominantly involved in DNA binding. 2-Haloacetaldehydes, formed from the 2-haloethylene oxides by halogen migration rearrangement, are the primary metabolites binding to protein and glutathione. The 2-haloacetaldehydes, being the more stable intermediates, probably play a significant role in binding to sites outside of the hepatocyte. (22 Refs)

OTHER METABOLISM OF CARCINOGENS

22. THRESHOLD LEVELS IN TOXICOLOGY: SIGNIFICANCE OF INACTIVATION MECHANISMS.

Greim H, Andrae U, Goggelmann W, Hesse S, Schwarz LR, Summer KH
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Adv Exp Med Biol; 136(partB):1389-1398 1982

Various in vitro test systems demonstrated that metabolic inactivation of chemicals may prevent toxic effects of reactive intermediates when present in low levels, while inactivation may be overcome at high levels. Reactive oxygen species formed during monooxygenase-mediated metabolism of chemicals can induce DNA repair activity in the human lymphoblastoid cell line NC37 BaEV. Addition of catalase, glutathione, and superoxide dismutase prevents hydroxyurea-induced DNA repair, indicating that H2O2 or reactive oxygen species deriving from H2O2 are likely to be genotoxic agents. Toxicity studies of chloroprene indicated that no carcinogenic effect could be found, while a slight mutagenic effect was noted with Salmonella typhimurium strains without metabolic activation. This finding is likely due to inactivation by glutathione-conjugations. In the presence of glutathione, chlorodinitrobenzene was not mutagenic in Salmonella typhimurium. However, at concentrations exceeding those of glutathione, it was increasingly mutagenic. Irreversible binding of naphthalene was increased by suppression of glucuronidation and sulfation in isolated hepatocytes. These findings demonstrate that two threshold doses can be observed: a no-effect level and a level at which the toxic effects disproportionally increase when high concentrations of a chemical are present and inactivation can be overcome. The relevance of extremely high doses often used in animal experiments for studying embryo toxicity or in other chronic toxicity studies is questioned. (25 Refs)

23. ROLES OF UDP-GLUCURONOSYLTRANSFERASE IN THE INACTIVATION OF BENZO(A)PYRENE.

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Adv Exp Med Biol; 136(partA):53-73 1982

Functional heterogeneity of uridine-5'-diphosphate-glucuronosyltransferase (UDP-GT), coordinate induction of 3-

methylcholantrene-inducible forms of cytochrome P-450 and UDP-GT1, and roles of UDP-GT in the metabolism of benzo(a)pyrene (BP) are discussed. On the basis of alterations of liver microsomal UDP-GT activity four groups of substrates can be distinguished. Tissue distribution of UDP-GT activities in microsomal fractions from different rat organs are presented. At least two functionally heterogenous forms of UDP-GT can be distinguished in rats and mice. UDP-GT1 and UDP-GT2 are characterized by differential induction of groups conjugation reactions by 3-methylcholanthrene and phenobarbital, respectively, and by separation and purification of these enzyme forms to apparent homogeneity. UDP-GT1 and UDP-GT2 activities show different developmental patterns and tissue distributions. UDP-GT1 shows high activity towards 3-hydroxybenzo(a)pyrene and BP-7,8-dihydrodiol. The conjugation of these intermediates may explain why in the presence of uridine-5'-phosphate-glucuronic acid, BP-monooxygenase activity is stimulated and BP mutagenicity in the Ames test (TA98) is decreased. The importance of conjugation reactions in the inactivation of BP metabolites is also observed in rat liver perfusion studies with BP when conjugation reactions are inhibited by salicylamide (SA). Mutagenicity in the medium is significantly increased under these conditions. In the absence of SA mutagenicity is low, suggesting efficient inactivation of BP by the liver. (45 Refs)

24. A NOVEL PATHWAY OF NITROSAMINE METABOLISM IN LIVER MICROSOMES: DENITROSATION OF NITROSAMINES BY CYTOCHROME P-450.

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Adv Exp Med Biol: 136(partB):1157-1164 1982

Denitrosation of nitrosamines by cytochrome P-450 (CP) and mechanistic aspects of nitrosamine denitrosation are discussed. The generation of nitrite in liver microsomes in vitro was shown to depend on N-nitrosomorpholine concentration and incubation time, and the reaction was markedly accelerated in liver microsomes from phenobarbital-pretreated animals. Nitrite formation was strongly inhibited by the addition of mono-oxygenase inhibitors, or by omission of NADPH. Pretreatment with 3-methylcholanthrene did not enhance denitrosation of nitrosamines in vitro. A strong correlation could be demonstrated between the rate of denitrosation of six different nitrosamines and their partition coefficients in CH_2Cl_2/H_2O. The generation of nitrite from dimethylnitrosamine was strongly inhibited by the addition of superoxide scavengers, superoxide dismutase and epinephrine. Nitrite formation was affected only by the addition of a very high dose (80 milliMoles) of mannitol or benzoate. No significant changes in nitrite production could be detected in H_2O_2-supplemented liver microsomes. NO-CP complex formation has also been observed in samples of nitrosamines and dithionite-supplemented liver microsomes. Thus under anaerobic conditions, reductive cleavage of the N-N bond might also occur. Proposed pathways of nitrosamine denitrosation ultimately result in the generation of primary amines and primary and secondary hydroxylamines. (9 Refs)

25. DENITROSATION OF CARCINOSTATIC NITROSOUREAS BY PURIFIED NADPH CYTOCHROME P-450 REDUCTASE AND RAT LIVER MICROSOMES TO YIELD NITRIC OXIDE UNDER ANAEROBIC CONDITIONS.

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Arch Biochem Biophys; 216(1):158-169 1982

Evidence establishing that the products of 2-chloroethyl nitrosourea denitrosation are nitric oxide (NO) and the parent urea is presented. NO formation during anaerobic microsomal denitrosation of 1,3-bis(-2-chloroethyl)-1-1-nitrosourea (BCNU) was demonstrated by determining NO binding to either ferrous cytochrome P-450 or hemoglobin which formed distinct Soret maxima at 444 and 415 nanometer, respectively. Further spectroscopic findings indicated that formation of the cytochrome P-450 ferrous-NO complex was catalyzed by NADPH-reduced microsomes. NO production during denitrosation of carmustine also was demonstrated by analysis of head gas of microsomal suspensions, which showed increasing NO concentrations with time. Determination of the cytochrome P-450 ferrous-NO optical extinction coefficient allowed the estimation of the denitrosation rates. Similar rates of ^{14}C-labeled 1-(2-chloroethyl)-3-(cyclohexyl)-1-nitrosourea (CCNU) denitrosation to form labeled 1-(2-chloroethyl)-3-(cyclohexyl)-1-urea were observed. ^{14}C-CCNU denitrosation by purified NADPH cytochrome P-450 reductase, noninhibited phenobarbital-induced microsomes and noninduced microsomes suggested a possible unique interaction of the NADPH cytochrome P-450 reductase and cytochrome P-450s in the cytochrome P-450 system. (40 Refs)

26. COOXIDATION OF THE CLINICAL REAGENT 3,5,3'5'-TETRAMETHYLBENZIDINE BY PROSTAGLANDIN SYNTHASE.

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Cancer Res; 42(7):2567-2570 1982

Prostaglandin synthase catalyzes the oxidation of arachidonic acid to prostaglandin H2 via a hydroperoxide intermediate, prostaglandin G2. The prostaglandin synthase system cooxidizes 3,5,3'5'-tetramethylbenzidine (TMB), a derivative of the human carcinogen benzidine, to colored products. This process is arachidonic acid dependent and indomethacin sensitive. The reaction is also supported by hydroperoxides, and, in this case, indomethacin has no effect. This suggests that the cooxidation is mediated by the hydroperoxidase activity of prostaglandin synthase. The products of TMB oxidation by this system are the same as those obtained with lactoperoxidase and H_2O_2 or with horseradish peroxidase and H_2O_2. The initial products of TMB oxidation are the TMB radical cation and a charge-transfer complex composed of TMB and its two-electron (diimine) oxidation product. The TMB radical cation was identified by electron spin resonance spectroscopy. Ascorbic acid reduces the products, regenerating the parent compound. (Author abstract) (22 Refs)

27. FURTHER CHARACTERIZATION AND APPLICATIONS OF THE 4-CHLOROBIPHENYL HYDROXYLASE ASSAY.

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Adv Exp Med Biol; 136(partA):753-759 1982

In vitro metabolism of 4-chlorobiphenyl (4-CBP) and benzo(a)pyrene (BP) were compared, and indirect evidence that these two chemicals share a common pathway of metabolism is presented. The putative binding of 4-CBP and BP to cytochrome P-450 was examined by room temperature difference spectrophotometry using freshly-prepared microsomes from 1-mo-old male Wistar rats. The apparent spectral dissociation constant (Ksapp) values indicated that cytochrome P-450 bound BP with a greater affinity than 4-CBP. Like the Ksapp values, the apparent Michaelis-Menten constant (Kmapp) values indicated that cytochrome P-450 bound BP more avidly than 4-CBP; the Kmapp values also showed that the binding affinity for both 4-CPB and BP was decreased slightly by phenobarbitone (PB) treatment but increased several-fold by 3-methylcholanthrene (MC) treatment. In noninduced, PB-induced, and MC-induced microsomes, 4-CBP was a competitive inhibitor of BP metabolism and vice-versa. The 4-CBP hydroxylase assay was used to show that 2,2',4,4',5,5'-hexachlorobiphenyl is a PB-type inducer. The 2,2',3,3',4,4'-hexachlorobiphenyl (2,3,4-HCBP) closely resembled a PB-type inducer; however, this isomer was a slightly more potent inducer of BP hydroxylase than PB and was a much more potent inducer of 4-CBP hydroxylase, suggesting that 2,3,4-HCBP has weak MC-type characteristics. The 2,2',3',4,4',5-hexachlorobiphenyl clearly differed from PB and exhibited marked MC-type characteristics, confirming prior reports that the isomer is a mixed (PB + MC)-type inducer. (17 Refs)

MODIFICATION OF CARCINOGEN METABOLISM

28. PROSTAGLANDIN ENDOPEROXIDE SYNTHETASE-DEPENDENT COOXIDATION OF (+-)-TRANS-7,8-DIHYDROXY-7,8-DIHYDROBENZO(A)PYRENE IN C3H/10T1/2 CLONE 8 CELLS.

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Cancer Res; 42(7):2628-2632 1982

The proximate form of the carcinogen benzo(a)pyrene, (+-)-trans-7,8-dihydroxy-7,8-dihydrobenzo(a)pyrene (BP-7,8-diol), is cooxidized during the oxidation of arachidonic acid to prostaglandins by prostaglandin endoperoxide synthetase (PES). This enzyme can oxidize BP-7,8-diol to the reactive intermediate (+-)-7beta,8alpha-dihydroxy-9alpha,10alpha-epoxy 7,8,9,10-tetrahydrobenzo(a) pyrene, which binds covalently to macromolecules, is mutagenic in bacterial test systems, and forms 7,8,9,10-tetrahydroxy-7,8,9,10-tetrahydrobenzo(a)pyrene (BP-tetrol) isomers. We have examined the cooxidation of BP-7,8-diol in an intact cell culture system of C3H/10T1/2 clone 8 mouse embryo fibroblasts, in which both the mixed-function oxidase and PES systems are present. When BP-7,8-diol is incubated for 72 hr with approx 10(6) confluent cells, high-performance liquid chromatography analysis of the organic extractable products reveals all four pairs of BP-tetrols, with those from (+-)-7beta,8alpha-dihydroxy-9alpha,10alpha-epoxy 7,8,9,10-tetrahydrobenzo(a) pyrene predominating. The addition of arachidonic acid (100 uM) produced a two- to three-fold increase in the formation of BP-tetrols from (+-)-7beta,8alpha-dihydroxy-9alpha,10alpha-epoxy 7,8,9,10-tetrahydrobenzo(a) pyrene, while the metabolism to BP-tetrols from (+-)-7beta,8alpha-dihydroxy-9beta,10beta-epoxy-7,8,9,10 tetrahydrobenzo(a) pyrene was unchanged. The addition of the PES inhibitor indomethacin (100 uM) completely eliminated this stimulation. Cell transformation assays were carried out under the same conditions. The addition of arachidonic acid resulted in a 10-fold increase in foci formation, while indomethacin inhibited the increase in foci formation by 70%. These results suggest that cooxidation of BP-7,8-diol to reactive intermediates by PES can occur in an intact cell system if stimulated with arachidonic acid. In addition to mixed-function oxidase-dependent activation of carcinogens, the cooxidation of chemicals to reactive metabolites during prostaglandin biosynthesis may also play a role in carcinogenesis. (Author abstract) (26 Refs)

29. EFFECT OF THE INSECTICIDES TOXAPHENE AND CARBARYL ON INDUCTION OF LUNG TUMORS BY BENZO(A)PYRENE IN THE MOUSE.

Triolo AJ, Lang WR, Coon JM, Lindstrom D, Herr DL
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J Toxicol Environ Health; 9(4):637-649 1982

The modulating effects of toxaphene (TOX) and carbaryl (CAR) upon benzo(a)pyrene (BP)-induced lung tumors and on BP hydroxylase activity in liver and lung were investigated. Female A/J mice were fed TOX (100 or 200 ppm) or CAR (1,000 ppm) in the diet, and administered 3 mg BP po on day 7 and day 21. No control animals or animals fed TOX alone but all BP induced and BP-induced plus TOX animals developed forestomach tumors at 12 wk. These tumors were well-developed squamous cell papillomas. While TOX alone produced no effect upon spontaneous lung tumors, feeding 100 ppm TOX to BP-induced animals caused a slight but statistically significant decrease in the incidence of lung tumors. The higher dose TOX, however, had no effect. Both TOX doses increased BP hydroxylase activity in liver but decreased it in lung. Combined TOX plus BP followed a similar pattern. Although feeding 200 ppm TOX for 20 wk alone did not affect lung tumor incidence in BP-treated mice, it markedly decreased the mean number of tumors per mouse and the percent of BP-induced lung tumors. Feeding 1,000 ppm CAR caused a modest increase in the incidence of BP-induced lung tumors. In a second experiment, however, no significant differences in lung tumor incidence were observed between controls and CAR-fed mice. Feeding CAR with BP did not affect liver BP hydroxylase activity but did significantly increase the activity of this enzyme in the lung. (47 Refs)

30. STUDIES ON THE MECHANISM OF STIMULATION OF MICROSOMAL H2O2 FORMATION AND BENZO(A)PYRENE HYDROXYLATION BY SUBSTRATES AND FLAVONE.

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Adv Exp Med Biol; 136(partA):179-198 1982

The effects of substrates of microsomal hepatic mixed function oxidase cytochrome P-450 (CP450) on microsomal

NADPH-dependent H2O2 formation, mechanism proposed for the interaction of substrate and NADPH in the activation of H2O2 formation, and the possible contribution of H2O2 to the in vitro activation of mixed function oxidation reaction are discussed. Modification by activators rather than by 'uncouplers' causes increases in NADPH oxidation, H2O2 formation, and hydroxylation reaction. Increased interaction of reductase and CP450 is at least as much responsible as 'uncouplers' for the increase in H2O2 formation. Microsomes were incubated with increasing concentrations of NADPH and hexobarbital or flavone to investigate the effects of activators. Results indicated that optimal H2O2 formation requires the stoichiometric presence of both NADPH and substrate. Changes in substrate-NADPH concentration alter the concentration of the functionally active complexes, and thereby the oxidase activity. The effect of inversely varied ratios of NADPH and flavone on benzo(a)pyrene (BP) metabolism was investigated. Maximal BP hydroxylation was obtained when flavone was high and NADPH low. Direct contribution of H2O2 in the metabolism of BP to phenolic metabolites might explain the observed difference. The maximal effects of flavone on BP hydroxylation suggest that the magnitude of electron flow appears to be important for the participation of either monoxygenase reactions, favored at high NADPH concentrations, or peroxidatic reactions, prevalently operative at low NADPH, but high flavone concentrations. (45 Refs)

31. INHIBITION OF RAT HEPATIC MICROSOMAL EPOXIDE HYDRASE BY HEAVY- AND ORGANOMETALS IN VITRO.

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Dept. Physiology, Univ. Turku, Turku, Finland
Adv Exp Med Biol; 136(partA):729-738 1982

Advantageous conditions for estimation of the relative inhibitory potencies of metal ions on epoxide hydrase were investigated, and the effects of some organic derivatives of the inhibitory metals were tested as inhibitors of epoxide hydrase. Epoxide hydrase activity was measured with styrene oxide and benzo(a)pyrene 4,5-oxide as substrates. Hydration of benzo(a)pyrene 4,5-oxide was much more sensitive toward inhibition by silver, mercury and cadmium, and to a lesser extent by copper, than hydration of the styrene oxide; the inhibition was dependent upon the microsomal amount present. (39 Refs)

32. DIETARY SELENIUM, HEPATIC ARYLHYDROCARBON HYDROXYLASE AND MUTAGENIC ACTIVATION OF BENZO(A)PYRENE, 2-AMINOANTHRACENE AND 2-AMINOFLUORENE.

Gairola C, Chow CK
Tobacco and Health Res. Inst., Lexington, KY, 40506
Toxicol Lett; 11(3/4):281-287 1982

Young (5-6 wk old) and adult (66 wk old) male Sprague Dawley rats were maintained on a low selenium (Se) basal diet with or without 1 or 2 ppm Se supplement for 5 or 20 wk. Five days prior to sacrifice, the animals were injected ip with Aroclor to determine aryl hydrocarbon hydroxylase (AHH) inducibility. Using the Ames Salmonella/microsome mutagenicity assay, the activation potential of the liver postmitochondrial supernatant was determined using benzo(a)pyrene (BP), 2-amino-fluorene (2AF) and 2-acetyl aminofluorene (2AAF) as potential mutagens. Low dietary Se caused a reduced AHH level in young control rats but dietary Se had no effect on AHH inducibility in both dietary groups. Since Se is a cofactor for glutathione peroxidase (GSH-P), the levels of GSH-P were decreased more in young rats by low dietary Se. Dietary Se did not appreciably affect the activation of BP, while low dietary Se affected the mutagenic activation of 2AF and 2AAF. (24 Refs)

33. STIMULATION OF DRUG AND CARCINOGEN METABOLISM BY PROLONGED ORAL TOBACCO CONSUMPTION.

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Biochem Pharmacol; 31(8):1595-1597 1982

Oral administration of tobacco to rats for 21 days caused remarkable stimulation of the metabolism of phenacetin, aniline and benzo[a]pyrene, a carcinogen, by hepatic microsomal mixed function oxidases (MFO). Such treatment for 6 days resulted in a small increase in the activities of phenacetin O-dealkylase and aromatic hydrocarbon hydroxylase (AHH) without affecting aniline hydroxylase activity. Nicotine given orally was found to be a relatively weak inducer of phenacetin O-dealkylase and aniline hydroxylase, and elicited a maximum increase in their activities within 6 days which remained unchanged even after 21 days of continuous administration. However, these two enzyme systems were not affected following only one or two doses of tobacco and nicotine. Both tobacco and nicotine inhibited these biotransformations in vitro. (Author abstract) (15 Refs)

34. METABOLIC ACTIVATION OF BENZO(A)PYRENE BY TRANSFORMABLE AND NONTRANSFORMABLE C3H MOUSE FIBROBLASTS IN CULTURE.

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Cancer Res; 42(7):2697-2704 1982

Incubation of 2.5 uM benzo(a)pyrene (BaP) with C3H/10T1/2 or CVP3SC6 (CVP) mouse fibroblasts from 48 hr resulted in the metabolism of 36 to 42% of the BaP to organic soluble derivatives, which cochromatographed with 7,8-trans-dihydroxy-7,8-dihydrobenzo(a)pyrene, 9,10-trans-dihydroxy-9,10-dihydrobenzo(a)-pyrene, 3-hydroxybenzo(a)pyrene, and 9-hydroxybenzo(a)pyrene, or to water-soluble derivatives. The formation of both organic and water-soluble metabolites during the 48-hr period increased proportionally with time, except in the case of BaP phenols, which increased initially but then remained the same or decreased. The distribution of organic soluble metabolites in the extracellular culture medium consisted primarily of BaP diols and was significantly different from that found inside the cells. The intracellular profile of organic soluble metabolites produced by both cell lines consisted predominantly of BaP phenolic derivatives and was qualitatively similar to the spectrum of metabolites produced by the incubation of BaP with C3H/10T1/2 or CVP cell microsomes. The nature of the BaP water-soluble derivatives produced by the C3H/10T1/2 and CVP cell lines was investigated by hydrolysis of culture medium with beta-glucuronidase and arylsulfatase. Although sulfation was not a major conjugation pathway for BaP in these cells, glucuronidation of BaP phenols was found to account for 30% of the total water-soluble derivatives. The similarity in the kinetics and qualitative nature of the metabolism of BaP by C3H/10T1/2 and CVP cells indicates that both cell lines are equally capable of biosynthesizing the proximal carcinogen, 7,8-trans-dihydroxy-7,8-dihydrobenzo(a)pyrene. Analysis of the water-soluble metabolites produced by these cells suggests further that the nonresponsiveness of the CVP cells to BaP-induced transformation cannot be accounted for on the basis of an increased detoxication of 7,8-trans-dihydroxy-7,8-dihydrobenzo(a)pyrene. (Author abstract) (34 Refs)

35. BENZO(A)PYRENE METABOLISM IN PRIMARY CULTURES OF MOUSE EPIDERMAL CELLS AND UNTRANSFORMED AND TRANSFORMED EPIDERMAL CELL LINES.

DiGiovanni J, Miller DR, Singer JM, Viaje A, Slaga TJ
Wistar Inst., Philadelphia, PA, 19104
Cancer Res; 42(7):2579-2586 1982

The metabolism of [3H]benzo(a)pyrene [B(a)P] by cultures of primary mouse epidermal cells and untransformed and transformed epidermal cell lines was investigated. All three cell types effectively metabolized [3H]B(a)P. The major organic solvent-extractable metabolites found intracellularly in primary cultures were trans-7,8-dihydro-7,8-dihydroxybenzo(a)pyrene and 3-hydroxybenzo(a)pyrene although quantities of 9-hydroxybenzo(a)pyrene, trans-9,10-dihydro-9,10-dihydroxybenzo(a)pyrene, and quinones also were present. The major organic solvent-soluble metabolites found in the extracellular medium were trans-9,10-dihydro-9,10-dihydroxybenzo(a)pyrene and trans-7,8-dihydro-7,8-dihydroxybenzo(a)pyrene, with smaller quantities of unconjugated phenols and quinones. The major water-soluble metabolites found in the extracellular medium were conjugated with glucuronic acid [primarily 3-hydroxybenzo(a)pyrene and several quinones]. No sulfate conjugates of [3H]B(a)P metabolites were detected. [3H]B(a)P metabolism was similar in cultures of untransformed and transformed epidermal cell lines but differed from the primary cultures. The major intracellular and extracellular organic solvent-soluble metabolites were diols. Little or no unconjugated phenols were detected. Both the untransformed and transformed epidermal cell lines converted [3H]B(a)P to water-soluble metabolites, primarily glucuronide conjugates. In contrast to the primary cells, a major pathway of trans-7,8-dihydro-7,8-dihydroxybenzo(a)pyrene metabolism in the untransformed and transformed cell lines was to a glucuronide conjugate. Primary mouse epidermal cells provide an important model system for studying factors affecting the activation and detoxification of hydrocarbon carcinogens. (Author abstract) (54 Refs)

36. HETEROGENEITY IN THE RATE OF BENZO[A]PYRENE METABOLISM IN SINGLE CELLS: QUANTITATION USING FLOW CYTOMETRY.

Miller AG, Whitlock JP
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Mol Cell Biol; 2(6):625-632 1982

A flow cytometric method was used to quantitate heterogeneity in overall benzo(a)pyrene (BP)-metabolizing activity among the cells of a population of Hepa-1c1c7 mouse hepatoma cells, and to assess the heterogeneity within variant cell populations with decreased ability to metabolize BP. The activity of the BP-metabolizing enzyme system was induced by exposure of the cell to 1 nanoM 2,3,7,8-tetrachlorodibenzo-p-dioxin for either 2 hr or 18 hr. The fluorescence-activated cell sorter was used in conjunction with the BP disappearance assay to analyze BP metabolism at the cellular level and to isolate both high- and low-activity variants in BP metabolism. The present method is much more rapid than subcloning and generates a more representative result, since many more cells may be studied. The individuals of a cloned population exhibited heterogeneity in metabolism of BP. Low-activity variants also exhibited a propensity to become heterogeneous in BP metabolism, an inherent property and not resulting from accumulation of new variants. Heterogeneity developed rapidly and in the absence of any mutational stress. (25 Refs)

37. MODULATION OF MICROSOME-MEDIATED BENZO[A]PYRENE-METABOLISM BY SERUM.

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Carcinogenesis; 3(4):359-362 1982

The effects of serum on the metabolism of benzo[a]pyrene (BP) by liver microsomes from 3-methylcholanthrene-treated rats were studied. In the presence of serum, the aryl hydrocarbon hydroxylase activities were enhanced to 160-570% of the control value. Enhancement of BP-metabolism by serum was also revealed by high performance liquid chromatography, but the relative amounts of a series of BP-metabolites were not changed appreciably by addition of serum. Binding of BP-metabolites to DNA was influenced by serum: adducts derived from two stereo-isomeric BP-7,8-dihydrodiol-9,10-oxides were increased, while those from 9-hydroxybenzo[a]pyrene-4,5-oxide were reduced. (Author abstract) (18 Refs)

38. ABSENCE OF INDUCTION OF ARYL HYDROCARBON HYDROXYLASE IN MICE AFTER TOPICAL APPLICATION OF BECLOMETHASONE DIPROPIONATE.

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Res Commun Chem Pathol Pharmacol; 36(2):319-327 1982

The effects of topical application of beclomethasone dipropionate (a corticosteroid) on the aryl hydrocarbon hydroxylase (AHH) activity in epithelial tissue (lung and skin) were studied. To evaluate the results of the pre-treatment with beclomethasone dipropionate a comparison was made with the effects of the topical application of benzanthracene (a polycyclic aromatic hydrocarbon and a known inducer of AHH activity). AHH activities were increased 2.5 to 5-fold in lung and about 20-fold in skin of mice after topical application of benzanthracene. However, after pre-treatment with beclomethasone dipropionate no induction of AHH activity could be observed, either in lung or in skin. The implications of these findings are discussed. (Author abstract) (8 Refs)

39. MONOOXYGENASE AND EPOXIDE HYDROLASE REGULATION IN PRIMARY FETAL RAT LIVER CELL CULTURE.

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Adv Exp Med Biol; 136(partA):87-98 1982

Presence of cytochrome P450 (CP450) was studied in fetal hepatocyte culture and measurements of aryl hydrocarbon hydrolase (AHH), ethoxycoumarin deethylase, aldrin epoxydase, and epoxide hydrolase (EH) activities were measured. The level of CP450 content in primary fetal liver cell culture was stable and did not significantly differ from that found in fetal liver used for the culture preparation. High concentration of phenobarbital (PB) induced both AHH and EH activities, whereas benz(a)anthracene acted preferentially , and 2,3,7,8-tetrachlordibenzo-p-dioxin selectively on AHH activity. AHH and EH activities were modified by addition of dexamethasone. The enzyme activities were first inhibited and then induced when the corticoid concentration was raised from 10(-10) to 10(-4) M. The same shift in the AHH inhibition in vitro by alpha-naphtoflavone (ANF) and metyrapone (MTR) was observed, whether the dexamethasone treatment was carried out in the presence or in the absence of serum. The action of other hormonal steroids on both AHH and EH activities was also studied. The same effect was observed with hydrocortisone: a shift in sensitivity of the control and PB-induced AHH activity in vitro from ANF to MTR, and a fall in the control and PB-induced EH activity. Sex hormones, testosterone (TS) and estradiol (ED) slightly induced the AHH activity and decreased the extent of AHH and EH induction by PB. TS and ED did not decrease the EH activity and did not shift in vitro the sensitivity of either the control or the PB-induced AHH to the inhibitors. According to these observations, glucocorticoids are some of the physiological stimuli controlling the expression of drug metabolizing enzyme activities in the perinatal period of life. (21 Refs)

40. DISSOCIATION OF 12-O-TETRADECANOYLPHORBOL-13-ACETATE AND 3-METHYLCHOLANTHRENE-INDUCED INDUCTION IN ORNITHINE DECARBOXYLASE AND ARYL HYDROCARBON HYDROXYLASE ACTIVITIES IN C57BL/6 MOUSE DERMAL FIBROBLASTS IN CULTURE.

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Cancer Lett; 16(1):25-31 1982

The effects of 3-methylcholanthrene (MC) on ornithine decarboxylase activity and of 12-O-tetradecanoylphorbol-13-acetate (TPA) on aryl hydrocarbon hydroxylase activity (AHH) in fibroblasts derived from polycyclic aromatic hydrocarbon-responsive C57BL/6 (B6) mouse dermis were investigated. While addition of TPA induced ODC activity eight-fold at 6 hr, inclusion of 2 uM MC had no effect on ODC activity. MC did, however, enhance AHH activity about five-fold at 24 hr, whereas TPA had no effect on AHH activity. Inclusion of DL-alpha-difluoromethyl ornithine (DFMO), a highly selective, irreversible inhibitor of ODC in the medium resulted in about 90% inhibition of ODC activity without affecting AHH activity. Inhibitors of microsomal monooxygenase (alphanaphthoflavone and SKF 525 A) inhibited AHH induction by 80% and 30% and ODC induction by 73% and 100%, respectively. Indomethacin enhanced ODC activity while slightly inhibiting AHH induction. Differential sensitivity of these two enzymes to cycloheximide was also observed. Exposure of cells to DFMO resulted in a near total abolition of ODC activity, while the inducibility of AHH was not affected. ODC and AHH induction processes are thus independent of each other. (20 Refs)

41. IN VITRO INHIBITION OF LIVER MICROSOMAL ARYLAMIDE N-HYDROXYLASE.

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Adv Exp Med Biol; 136(partB):1203-1211 1982

In vitro effects of various chemicals on the liver microsomal (LM) N-hydroxylase (NH) activity from control or 3-methylcholanthrene (3-MC) pretreated rat, hamster, and mouse are discussed. Pretreatment with 3-MC induces NH activity in all three species: 30-fold in rat, 12-fold in hamster, and 5-fold in mouse. Submicromolar concentrations of 3-MC, 7,8-benzoflavone, and benzo(a)pyrene inhibit LM 2-acetylaminofluorene (2-AAF) NH from both control and 3-MC pretreated hamster, rat, and mouse. Inhibitor of microsomal deacetylase, paraoxon, also inhibited NH of rat, hamster, and mouse microsomes. NH activity decreased progressively with increasing concentrations. At 5 uM of paraoxon, the enzyme activity (at 0.25 uM concentration of 2-AAF) was inhibited by 20%, at 50 uM by 70%, and at 200 uM by 85%. Strong inhibition of 2-AAF N-hydroxylation was observed with 1-acetylaminofluorene and 3-acetylaminofluorene, whereas 4-acetylaminofluorene had no such effect. The 1-and 3-isomers appeared thus to bind the enzyme. Added in vitro to the incubation medium (at 50 uM) norharman and harman inhibited the liver microsomal N-hydroxylation of 2-AAF (0.25 uM). Liver microsomes from both control and 3-MC treated rat, hamster, and mouse were all sensitive to the inhibition which varied from 60% for rat to 80% for hamster and mouse. The effect of harman was dose-dependent. Results indicate that the mouse appeared to be most effective in N-hydroxylating 2-AAF. (16 Refs)

42. IN VIVO METABOLISM OF 3-METHYLCHOLANTHRENE (MC) IN PREGNANT C57BL/6 AND DBA/2 MICE (MEETING ABSTRACT)

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Toxicologist; 2(1):25 1982

MC has been linked to carcinogenesis in laboratory animals and their transplacentally exposed offspring. Activation of MC to reactive intermediates is catalyzed by microsomal aryl hydrocarbon hydroxylase (AHH), the activity of which correlates positively with tumorigenesis. This study compares the in vivo metabolic profiles of MC in the maternal and fetal tissues of C57BL/6 (high AHH) and DBA/2 (low AHH) mice. Maternal liver, placenta, and whole fetuses from pregnant mice exposed to 14C-MC were evaluated for extractable and bound 14C activity. HPLC (high performance liquid chromatography) analyses of ethylacetate extracts revealed no qualitative differences in the spectrum of metabolites found in the tissues of either strain of mouse; seven metabolites, in addition to MC, have been identified. In both strains, the placenta appears to be acting as a reservoir for the parent compound. The free MC metabolite profiles of the two strains of mice differ quantitatively for all tissues studied. Tissues from DBA/2 mice contained higher relative levels of MC, which is consistent with the lower AHH activity of this strain. Two additional regions of 14C activity have been tentatively identified through HPLC and alumina column chromatography as conjugates of the free metabolites. In the non-extractable tissue residue from both strains, the 14C activity was primarily associated with the lipid and protein fractions, although some activity was associated with RNA, DNA, glucosaminoglycan, and carbohydrate. Findings to date indicate that the major difference in the metabolic profiles of MC in C5BL/6 and DBA/2 mice is in the level of metabolism and not in the types of metabolites produced. (no Refs)

43. THE EFFECT OF SUBSTRATES AND INHIBITORS OF MONOAMINE OXIDASE (MAO) ON HEPATIC DIMETHYLNITROSAMINE (DMN) METABOLISM AND MUTAGENICITY IN THE AMES TEST (MEETING ABSTRACT)

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Toxicologist; 2(1):172 1982

Dimethylnitrosamine (DMN), a potent hepatocarcinogen and mutagen, requires metabolic activation to exert its biological effects. Although it has been suggested that hepatic DMN metabolism is catalyzed by cytochrome P-450 dependent mixed function oxidase (MFO) enzymes, recent studies have provided evidence for several pathways of DMN metabolism. We have investigated the effect of a number of substrates and inhibitors of monoamine oxidase (MAO, EC 1.4.3.4) on DMN metabolism and DMN-induced mutagenicity. The metabolism of DMN for formaldehyde by rat hepatic postmitochondrial supernatant fractions was markedly inhibited by a number of MAO inhibitors (eg aminoacetonitrile, benzyl cyanide, indazole and pargyline) and by MAO substrates (eg benzylamine, 2-phenylethylamine, tryptamine and tyramine), but not by the deaminated aldehyde, acid and alcohol products of the latter class of compounds. At the concentrations which inhibited DMN metabolism the MAO substrates and inhibitors had little effect on a range of MFO enzyme activities. While the mutagenicity of DMN in the Ames test was markedly inhibited by MAO substrates and inhibitors, these compounds had little effect on the mutagenicity of either aflatoxin B1 or benzo(a)pyrene. (no Refs)

44. THE EFFECT OF SUBSTRATES AND INHIBITORS OF MONOAMINE OXIDASE ON HEPATIC DIMETHYLNITROSAMINE METABOLISM AND MUTAGENICITY.

Lake BG, Rowland IR, Harris RA, Collins MA, Phillips JC, Cottrell RC, Gangolli SD
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Adv Exp Med Biol; 136(partB):1143-1147 1982

Inhibition of both dimethylnitrosamine (DMN) metabolism and DMN-induced mutagenesis by substrates and inhibitors of monoamine oxidase (MAO) was studied using hepatic postmitochondrial supernatant fractions from male Sprague-Dawley rats. The addition of aminoacetonitrile and isoxazole markedly inhibited the metabolism of DMN to formaldehyde. However, both compounds had little effect on the activities of the two mixed function oxidase (MFO) enzymes ethylmorphine N-demethylase and aniline 4-hydroxylase. Similarly, benzimidazole and indazole inhibited the metabolism of DMN but not that of the two MFO substrates. DMN metabolism was also inhibited by the addition of the MAO substrates 2-phenylethylamine, tryptamine, and tyramine but not by cadaverine which is a substrate of diamine oxidase. Both MAO substrates and inhibitors were potent inhibitors of DMN-induced mutagenesis in the Ames test, whereas cadaverine had no effect. Neither MAO substrates nor MAO inhibitors had any marked effect on the mutagenesis of either aflatoxin B1 or benzo(a)pyrene. Both these carcinogens are considered to be metabolically activated by enzymes of the MFO complex. Results demonstrated that a number of compounds of diverse chemical structures inhibit the metabolism and mutagenesis of DMN at concentrations which had little effect on several cytochrome P-450 dependent processes. As these compounds are either known substrates or inhibitors of MAO the results may suggest the participation of an enzyme with MAO-like properties in the hepatic metabolism/bioactivation of this nitrosoamine. (16 Refs)

45. ANDROGEN REGULATION OF DMN-N-DEMETHYLASE ACTIVITY IN KIDNEY OF BALB/C MICE (MEETING ABSTRACT)

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Med Pediatr Oncol; 10(1):102 1982

Androgenic hormones have been shown to regulate the biotransformation of Dimethylnitrosamine (DMN) to its active mutagenic metabolite. This androgenic regulation in renal tissue is a receptor mediated phenomenon as androgens are not able to stimulate kidney microsomal enzymes required for Ames test, in Tfm mice. Further, even though hepatic enzymes are more active than the kidney enzymes, the androgen effect is tissue (kidney) specific. Recent observation indicates that this androgenic effect is observed only under conditions when androgen receptors are translocated in the nucleus. The present experiments were designed to test correlations between the mutagenic ability of renal tissue and its N-demethylase activity (an enzyme implicated in conversion of DMN to its active metabolite). N-demethylase activity was measured from micromosomal fractions of liver and kidney (by quantitating formaldehyde formation) according to Nash. The results indicate: (1) higher DMN-N-demethylase activity in liver (male or female, adults) compared to kidney (male or female); (2) higher enzyme activity in adult male compared to adult female renal tissue; (3) complete loss of renal but not liver enzyme activity in mice castrated for 7 days (testosterone treatment, 2 mg/day/10 days, can significantly increase enzyme activity of kidney tissues in such castrates); and (4) a significant increase in DMN-N-demethylase activity in renal tissue of testosterone treated adult female mice. These data indicate androgenic regulation in kidney DMN-N-demethylase activity. The BALB/c mouse kidney system is a useful model to study the mechanism(s) by which steroid hormones augment or inhibit biotransformation of procarcinogens to mutagens which may ultimately lead to tumorigenesis. (2 Refs)

46. DRUG-NITRITE INTERACTIONS IN HUMAN SALIVA: EFFECTS OF FOOD CONSTITUENTS ON CARCINOGENIC N-NITROSAMINE FORMATION.

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J Dent Res; 61(6):768-771 1982

A simple and rapid high-pressure liquid chromatographic assay for monitoring N-nitrosodimethylamine (NDMA) in human saliva was developed. The method was used to study in vitro the effects of common food constituents on NDMA formation in saliva from the interaction of salivary nitrite with aminopyrine and oxytetracycline. Natural phenolic compounds, caffeic acid, and tannic acid, and synthetic additives, erythorbic acid, sorbic acid, propyl gallate, and butyrated hydroxytoluene - all inhibited NDMA formation (20-80%). With ascorbic acid, up to 90% inhibition of NDMA synthesis in saliva was observed. In contrast, chlorogenic acid (a phenolic component of coffee) acted as a catalyst (up to 48% increase) of the nitrosamine formation under identical experimental conditions. (Author abstract) (21 Refs)

47. MICROSOMAL METABOLISM OF 2-ACETYLAMINOFLUORENE, ROLE IN MUTAGENICITY AND CARCINOGENICITY.

Roberfroid M, Razzouk C, Agazzi-Leonard E, Batardy-Gregoire M, Poncelet F, Mercier M

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Adv Exp Med Biol; 136(partB):921-929 1982

Biochemical properties of microsomal enzymes catalyzing endoplasmic reticulum-mediated metabolism of 2-acetylaminofluorene (2AAF), including reactions of primary activation and detoxification, were studied as means of elucidating the mechanism of biological effects of 2AAF. Correlation of kinetic parameters of liver microsomal N-hydroxylase with carcinogenic effects showed that the rat is the most susceptible species, but exhibited the lowest activity, whereas the mouse is the least susceptible species, but it has the highest enzyme activity. The rat liver microsomal N-hydroxylase showed the highest affinity for 2AAF, whereas the mouse liver enzyme had the lowest affinity. Mutagenicity of the animal microsomal preparations correlated well with their enzyme activities ranking in the order hamster = mouse much greater than rat in terms of the Ames test with 2AAF as a promutagen. Kinetic parameter studies with rat liver microsomal N-hydroxylase showed that 2AAF and 2-aminofluorene modified the enzyme, but other aminofluorene isomers did not. Feeding the rat with 2AAF and 3-methylcholanthrene (3MC) resulted in a competitive inhibition in the endoplasmic reticulum that reduced N-hydroxylating capacity. Similar behavior of 3MC in the hamster results in the initiation of cancer because the hamster liver N-hydroxylase activity is far higher than that of the rat liver enzyme so that there is production of sufficient N-hydroxy-metabolite to initiate cancer. (18 Refs)

48. ON THE LIKELY MECHANISMS BY WHICH CARCINOGENS INDUCED ADRIAMYCIN RESISTANCE IN RAT HEPATOCYTES (MEETING ABSTRACT)

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Twenty-third Annual General Meeting of the British Association for Cancer Research, March 29-31, 1982, Edinburgh Scotland. British Association for Cancer Research 78 pp., 1982.

Administration of the hepatocarcinogen 2-acetylaminofluorene (AFF) to rats induces a resistance in their hepatocytes to doses of adriamycin (Ad) that are cytocidal to normal hepatocytes after incubation in vitro in primary monolayer culture. To investigate the mechanism of this carcinogen-induced resistance, sensitive (normal) and resistant (2-AAF altered) hepatocytes were incubated with Ad 1.8 x 10-5M for periods up to 24 hrs. No differences were observed in the cellular uptake, efflux, DNA-binding, DNA nicks, or inactive Ad aglycone metabolites between sensitive and resistant cells. However, only 50% of the fluorescing material was organic extractable. Examination of the aqueous non-extractable material revealed that this comprised 13% of the total cellular fluorescence in the sensitive cells and 34% in the resistant cells. It contained mainly highly polar metabolites, presumably water-soluble conjugates. Administration of Ad mg/kg iv to normal or 2-AAF treated rats resulted in similar concentrations of Ad and % fluorescence in the non-toxic aglycone metabolites. No Ad-OH was observed. (1 Ref)

49. BENZIL, A SELECTIVE INDUCER AND POTENT IN VITRO ACTIVATOR OF MICROSOMAL EPOXIDE HYDROLASE.

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Adv Exp Med Biol; 136(partA):717-728 1982

Structural requirements and kinetics of epoxide hydrolase (EH) activation in vitro was studied using benzil (BZ) and the activating effect of BZ was compared to that of metyrapone (MP) and chalcone epoxide (CE). If the assay for EH was begun immediately after the addition of BZ, the activation was considerably less than that obtained using preincubation. EH activity was linear for at least 10 min in the presence of BZ after preincubation. Maximal stimulation was observed between pH 7.0-8.0 using microsomes from untreated animals. Activation in the presence of BZ was greatly lowered by detergent triton X-100, and activations by MP and CE were also somewhat decreased. BZ affected both the apparent affinity of EH for styrene oxide as well as the maximal rate of catalysis. Structural requirements for activation were rather specific. When one of two keto groups in BZ was replaced by a hydroxyl group or a hydrogen, the activation was reduced from greater than 400% to 8% and 98%, respectively. When microsomes were incubated with different combinations of BZ, CE, and MP, in a concentration of 1.6 milliM, the EH activation obtained was always equal to that observed with one of the activators alone. BZ is a more specific inducer of EH than trans-stilbene oxide (TSO). No or little relationship was observed between the structural requirements for induction and activation. EH activity in liver microsomes from animals induced with phenobarbital, 3-methylcholanthrene, 2-acetylaminofluorene, TSO, or BZ could be activated in vitro to the same extent as the activity in control microsomes. (17 Refs)

50. THE CYTOCHROME P-450-MEDIATED METABOLISM OF BIPHENYL AND THE 4-HALOBIPHENYLS.

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Adv Exp Med Biol; 136(partA):745-752 1982

Effects of phenobarbitone (PB) and 3-methylcholanthrene (MC) on the metabolite profiles and overall rates of metabolism in vitro of 4-fluorobiphenyl (4FBP), 4-chlorobiphenyl (4CBP), 4-bromobiphenyl (4-BBP), and 4-iodobiphenyl (4-IBP) was reported. Also, the spectrally-apparent interaction of biphenyl (BP) and the 4-halobiphenyls with noninduced, PB-induced, and MC-induced rat hepatic microsomes was reported. Putative binding of BP and the 4-halophenyls to cytochrome P-450 was examined by room temperature difference spectrophotometry using freshly-prepared microsomes. The liver microsomes were prepared from 1-mo-old male Wistar rats. The rate of metabolism of BP, 4-FBP, and 4-BBP was increased 2x by PB and 4-6x by MC treatment. The rate of metabolism of 4-CBP and 4-IBP was not significantly increased by PB treatment but was increased by more than an order of magnitude by MC treatment. Both the magnitude of the absorbance change and the apparent binding affinity of cytochrome P-450 for BP and the 4-halobiphenyls increased with increasing substrate lipophilicity. The spectrally-apparent interactions failed to indicate any preferential binding of the substrates to either noninduced, PB-induced, or MC-induced microsomes. Thus, the reason for the differential effects exerted by the halogens remains unknown. (13 Refs)

51. THE ACTIVATING ROLE OF GLUTATHIONE IN THE MUTAGENICITY OF 1,2-DIBROMOETHANE.

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Adv Exp Med Biol; 136(partA):809-820 1982

Role of conjugation to glutathione (GSH) in the mutagenicity of 1,2-dibromoethane (DBE) was investigated and some preliminary results on the occurrence of reactive GSH conjugates in vivo are reported. The activity of GSH-S-transferase in vitro, synthesis and reactions of model conjugates, mutagenicity of DBE, and DNA binding of DBE are reviewed. DBE was tested to determine which mechanism is responsible for the activation. Results indicated that the enhancement of mutagenic activity is caused by conjugation to GSH. The spontaneous binding of DBE to DNA may result from initial reactions with sulfur or nitrogen nucleophiles, giving rise to the same type of half-mustards as the GSH conjugates. Rats excreted 30-50% of DBE in the form of mercapturic acid. Direct conjugation of GSH with DBE and DBE oxidation followed by loss of hydrogen bromide may lead to the structure of the metabolite. Excretion of N-acetyl-S-2-hydroxyethyl-L-cysteine by male Wistar rats after administration of 0.1 millimole DBE/rat with and without pretreatment with 10 g 1-phenylimidazole/rat is presented. Results show that direct conjugation of DBE to GSH and thus formation of the reactive 2-halogenothioether in vivo is a viable pathway of metabolization. Conjugation to GSH can give rise to the formation of reactive glutathione conjugates, provided a second leaving group is present at the carbon atom next to the one where sulfur substituent becomes attached. (21 Refs)

52. ASSESSMENT OF THE CAPACITY OF 3,3',4,4',5,5'-HEXABROMOBIPHENYL TO SERVE AS A PROMOTER OF HEPATOCARCINOGENESIS (MEETING ABSTRACT)

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Toxicologist; 2(1):99 1982

The objective of this study was to determine if 3,3',4,4',5,5'-hexabromobiphenyl (HBB) can act as a promoter of hepatocarcinogenesis. This congener and 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) are similar in that they both cause 3 methylcholanthrene type induction of hepatic microsomal drug-metabolizing enzymes and produce a similar and characteristic pattern of toxic and histologic responses. TCDD has been shown to be a promoter of hepatic cancer in rats. To test the tumor promoting capacity of HBB, female Sprague-Dawley rats weighing 200-250 g were injected ip with diethylnitrosamine (DEN) at a dose of 10 mg/kg 24 hours after a 2/3 partial hepatectomy (PH). Thirty days after PH, groups of 6 rats were fed control diets or diets containing 1 ppm HBB or 500 ppm phenobarbital (Pb). Groups of 3 rats without prior hepatectomy or DEN were fed the same diets. At 6 months, rats were killed and samples were collected for histologic and histochemical evaluation. Gamma glutamyl transpeptidase (GGT) was used to identify enzyme altered foci. The average number of GGT positive foci/cm2 were: control, 0; Pb, 58; HBB, 79. Values for rats not hepatectomized or given DEN were: control, 0; HBB, 11. Rats fed HBB had decreased weight gain and thymic atrophy. Histologically, the liver had severe hepatocellular swelling and vacuolation and focal areas of necrosis. (no Refs)

53. COMPARATIVE EFFECTS OF DIETARY ADMINISTRATION OF 2(3)-TERT-BUTYL-4-HYDROXYANISOLE AND 3,5-DI-TERT-BUTYL-4-HYDROXYTOLUENE ON SEVERAL HEPATIC ENZYME ACTIVITIES IN MICE AND RATS.

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Cancer Res; 42(7):2609-2615 1982

Effects of feeding mice and rats with 2(3)-tert-butyl-4-hydroxyanisole (BHA) and 3,5-di-tert-butyl-4-hydroxytoluene (BHT), have been compared to search for common effects between the two agents in two different rodent species and then applied toward better understanding of the mechanisms involved in their protective actions. Common effects could not be recognized at the microsomal mixed-function oxidase level. Contrary to expectations based on chemical structures, BHT feeding elevated the epoxide hydrolase activity to an even greater extent than that produced by BHA, especially in rats. However, enzyme activities involved in the glucuronide conjugation system are all elevated by both antioxidants in both rodent species. With BHA treatment, the levels of acid-soluble thiols were increased in both rats and mice. However, with BHT, the level was increased only in mice but not in rats. Similar trends were produced for glucose-6-phosphate dehydrogenase activity, but glutathione reductase activity was increased even for BHT-treated rats. Additionally, the glutathione S-transferase activities were also increased by both antioxidant treatments and in both rodent species. Based on these results, the elevations of epoxide hydrolase activity along with the enhanced glucuronide conjugation and glutathione oxidation-reduction conjugation system enzyme activities were common to both compounds in both rodent species. This suggests their involvement in anticarcinogenic mechanisms. Increases of these detoxification enzyme activities appeared to be all designed to accelerate the elimination of administered antioxidants but, inadvertently, conferring protective effects from xenobiotics such as carcinogens. (49 Refs)

54. L-AZASERINE INDUCTION OF LAMBDA PROPHAGE: ENHANCING ACTIVITY OF TISSUE EXTRACTS FROM NORMAL AND DIETARY METHYL GROUP DEFICIENT RATS (MEETING ABSTRACT)

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Department of Biology and Nutrition, M.I.T., Cambridge, MA
Toxicologist; 2(1):123 1982

L-azaserine is a potent carcinogen that, in bacteria, can cause mutation and bacteriophage induction without prior activation by mammalian enzymes. However, we found that rat tissue extracts markedly enhanced azaserine phage inducing activity. In the Inductest of Moreau, et al, prophage induction in Escherichia coli (lambda) by azaserine alone began only after a 40-60 minute lag. Addition of rat hepatic post mitochondrial supernatant (S9) enhanced induction by reducing the lag; more than 50% of the population was induced by 40 minutes. Preparations from rats fed a diet deficient in methyl groups were about twice as effective in the enhancement of induction at a given time as S9 fractions from control animals. Enhancing activity was found also in pancreatic extracts, but in lesser amount than in liver and was unaffected by diet. Most of the S9 activity was found to be in the cytosol; it was destroyed by trypsin. Hepatic cytosol enhanced also azaserine mutagenesis in Salmonella typhimurium, at short times of exposure. Under Inductest conditions cytosol promoted incorporation of label from 14C-azaserine into the bacteria, most of it into acid insoluble material, usually after a 15-20 minute lag. This pattern differed from the rapid active transport and incorporation of the amino acids tryptophan and proline into bacteria that was not affected by cytosol. (no Refs)

55. BIOCHEMICAL BASIS FOR IMPAIRED DRUG METABOLISM IN TUMOR-BEARING RATS EVIDENCE FOR ALTERED REGULATION OF HEPATIC MICROSOMAL HEMEPROTEIN SYNTHESIS.

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Biochem Pharmacol; 31(8):1535-1543 1982

The pharmacologic effects of many drugs are enhanced in animals bearing tumors. This apparently stems from a decrease in the microsomal metabolism of these compounds in liver cells, owing to a decrease in either the activities of certain enzymes or in the content of cytochrome P-450 in microsomes, or both. Since impaired drug metabolism may have a direct bearing on the outcome of chemotherapy, a study of the biochemical basis for this alteration was begun. In female Sprague-Dawley rats bearing Walker 256 solid tumors im, pentobarbital metabolism was impaired as judged from prolonged sleeping-times. This effect was accompanied by a decrease in the microsomal content of cytochrome P-450. Analysis of hepatic microsomes by sodium dodecylsulfate-polyacrylamide gel electrophoresis revealed that a microsomal protein of approx 53,000 daltons was diminished in livers of tumor-bearing animals when compared to normal controls. When rats were injected with [3H]leucine, approx 40% less 3H was associated with the microsomal proteins in the cytochrome P-450 region of tumor-bearing animals than with those of normal controls. This was attributed to a decrease in the rate of synthesis of these, but not of other, microsomal proteins. The overall content of microsomal hemeproteins of tumor-bearing rats was reduced considerably, when compared to normal controls. We found that in the livers of 7-day tumor-bearing rats, the activity of delta-aminolevulinic acid synthetase was only 16% of control activity; conversely, the activity of hepatic microsomal heme oxygenase in the tumor-bearing rats was nearly 8x greater than that of the normal animals. Together, these data indicate that perturbations in heme- and hemeprotein-synthesis caused the reduced content of cytochrome P-450 seen in tumor-bearing rats, and they provide partial explanation for diminished drug metabolism by hepatic microsomes in the presence of a growing, transplantable, non-hepatic tumor. (54 Refs)

MUTAGENICITY OF ACTIVATED METABOLITES OF CARCINOGENS

56. DIFFERENTIAL ABILITY OF AMBYSTOMA TIGRINUM HEPATIC MICROSOMES TO PRODUCE MUTAGENIC METABOLITES FROM POLYCYCLIC AROMATIC HYDROCARBONS AND AROMATIC AMINES.

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Cancer Lett; 16(1):33-41 1982

The ability of salamander hepatic microsomal mixed function oxygenases to metabolize benzo(a)pyrene (BP), perylene and the aromatic amines 2-aminoanthracene (AA), 2-aminofluorene (AF), 2-acetylaminofluorene (AAF), 4-amino-trans-stilbene (AS), monoacetylbenzidene (MAB), and diacetylbenzidine (DAB), to chemical species capable of inducing revertants in Salmonella typhimurium was investigated. Microsomal enzyme preparations from the livers of Aroclor-induced salamanders mediated the activation of AA, AF, AAF, AS, MAB, and DAB. Benzidene and 4-aminobiphenyl were poorly mutagenic in this system. The reactions were NADPH- and microsomal enzyme concentration-dependent. Rat microsomal enzyme induction with phenobarbital produced a marked increased in mutagenesis by benzidine, MAB, and DAB. However, phenobarbital was not a more effective inducer than Aroclor in the activation of these or other tested aromatic amines by salamander enzymes. No evidence was observed that BP or perylene were mutagenic after reaction with salamander liver microsomes. It is suggested that amphibian microsomal oxygenases may carry out N-oxidation more efficiently than C-oxidation. (30 Refs)

57. SISTER CHROMATID EXCHANGE INDUCTION IN TWO CELL LINES.

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Environ Mutagen; 4(3):267-270 1982

In the absence of the S9 metabolizing system, benzo(a)pyrene induced sister chromatid exchanges (SCE) in Chinese hamster lung (Don) cells but not in Chinese hamster ovary cells (CHO). Addition of S9 to CHO cells is necessary to obtain levels of SCE/metaphase similar to those induced in Don cells. It is suggested that Don cells still have an intact intracellular enzyme system capable of metabolizing biologically inert compounds into an active form. (12 Refs)

58. SISTER CHROMATID EXCHANGE RESPONSE OF HUMAN DIPLOID FIBROBLASTS AND CHINESE HAMSTER OVARY CELLS TO DIMETHYLNITROSAMINE AND BENZO(A)PYRENE.

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Environ Mutagen; 4(3):203-214 1982

A study was undertaken to examine the possibility that Chinese hamster ovary (CHO) and human diploid fibroblasts may not show the same sensitivity to well known carcinogens benzo(a)pyrene (BP) and dimethylnitrosamine (DMN), using a metabolic activation system and sister chromatid exchange (SCE) analysis. Metabolic activation in the tests was accomplished with a microsomal fraction from rats induced with Aroclor 1254. The human diploid lines employed were IMR-90, WI-8, and S-3299. For both BP and DMN the human cells and CHO cells showed dose-response slopes that were significantly different from zero, except for CHO cells treated with BP for 1 hr and S-3299 cells treated with DMN. While the responses of the human and CHO cells to BP, and the responses of the human cells to BP and DMN were similar, the dose-response of the human cells to DMN was statistically less significant than that of CHO cells. Reducing the period of treatment of CHO cells from 1.0 hr to 0.5 hr had no effect on the slope of the dose-response curves for BP and DMN. The observed differences between human and CHO cells may reflect differences in the fate of metabolic intermediates of DMN. (38 Refs)

59. FATE OF EPOXIDES.

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Adv Exp Med Biol; 136(partA):39-52 1982

Structure-activity relationships for the mutagenicity of a series of closely related epoxides are described and control of reactive metabolites derived from closely related aromatic compounds by different enzymes is discussed. The mutagenicity of a homogenous series of 17 epoxides was studied using four tester strains of Salmonella typhimurium. In strains TA 100 and TA 1535, which are base-pair substitution mutants, 12 of the epoxides were detected as mutagens. A number of structurally similar 1,2-disubstituted oxyranes, which occur as structural units in a wide variety of drugs and natural compounds, are weak or moderate mutagens. The presence of the double bond in formal conjugation with the epoxide ring increased the mutagenicity relative to the saturated oxyrane. The mutagenicity of benz[a]anthracene investigated in the mammalian enzyme mediated Salmonella test was affected very differently by the same modifications of the metabolizing system, in spite of very similar chemical structures and physicochemical properties of the compounds studied. Microsomal epoxide hydrolase activity in different species towards three different substrates is presented. Epoxides are electrophilic reactive to varying degrees and can chemically react with nucleophilic tissue constituents thereby altering critical cellular macromolecules including DNA, RNA, and proteins. Non-enzymic rearrangement and several enzyme-catalyzed reactions compete with this covalent binding. (34 Refs)

60. MUTAGENICITY OF ANTHRAQUINONE AND HYDROXYLATED ANTHRAQUINONES IN THE AMES/SALMONELLA MICROSOME SYSTEM.

Liberman DF, Fink RC, Schaefer FL, Mulcahy RJ, Stark AA
Environmental Medical Service. Massachusetts Inst. Technology, Cambridge, MA, 02139
Appl Environ Microbiol, 43(6):1354-1359 1982

The mutagenicity of anthracene, anthraquinone, and four structurally similar compounds of each was evaluated in the Ames/Salmonella microsome assay. Anthraquinone was shown to be mutagenic for strains TA1537, TA1538, and TA98 in the absence of rat liver homogenate. The four anthraquinone derivatives tested were mutagenic for TA1537 exclusively. None of the anthracenes exhibited mutagenic activity. (Author abstract) (9 Refs)

61. MUTAGENIC ACTIVITY OF THREE ISOMERIC N-NITROSO-N-METHYLAMINO-PYRIDINES TOWARDS ESCHERICHIA COLI K-12 IN IN VITRO AND ANIMAL-MEDIATED ASSAYS.

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Carcinogenesis; 3(4):415-421 1982

Three isomeric nitrosomethylaminopyridines were tested in vitro and in the host-mediated assay for their activity to induce gene mutations in E coli K-12 strain 343/113. Nitrosodimethylamine (NDMA) and nitrosomethylaniline (NMA) were also tested. The in vitro mutagenicity tests were performed either without in the presence of various fractions (S-9, microsomes, S-100) of rodent liver homogenates. The in vivo mutagenicity was determined in host-mediated assays, in which the indicator E coli cells were recovered for the liver of treated animals. N-nitro-N-methyl-2-aminopyridine (2-NMPY) and N-nitro-N-methyl-4-aminopyridine (4-NMPY) were activated to mutagenic factors by microsomes, but their mutagenic effect was completely abolished when S-100 was added. N-nitro-N-methyl-3-aminopyridine (3-NMPY) was directly mutagenic for E coli but its mutagenic potential was abolished when S-100 liver fraction was added to the incubation mixtures. NDMA was activated to mutagenic factors with both microsomes and S-9 fractions, whereas NMA could not be shown as mutagenically active under any of the present experimental conditions. It could be shown that the deactivating effect of the S-100 fraction was of non-enzymatic nature, and probably was due to the presence of thiol-containing 'scavenger' molecules in this fraction. In the host-mediated assays, only the 2-isomer among the three exerted a mutagenic affect. The results indicate that the isomers investigated here are mutagenic either directly or upon microsomal activation. The non-carcinogenicity of 3-NMPY and 4-NMPY, and the non-mutagenicity of these compounds in host-mediated assays, is probably the result of very efficient deactivation by cytosolic (thiol-group-containing?) factors. (23 Refs)

62. COMPARISON OF MICROSOMAL INDUCER PRETREATMENT ON THE IN VITRO ALPHAHYDROXYLATION AND MUTAGENICITY OF N-NITROSOPYRROLIDINE IN RAT AND HAMSTER LIVER.

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Dept. Epidemiology and Community Health, Inst. for Environmental Health Sciences, Case Western Reserve Univ. Sch. Medicine, Cleveland, OH, 44106
Environ Mutagen; 4(3):221-230 1982

Reasonable agreement is demonstrated between rates of microsomal alpha-hydroxylation of N-nitrosopyrrolidine (NPYR) and the metabolic activation of NPYR to a mutagen by post-mitochondrial supernatants when changes in microsomal protein are taken into account. The Ames assay for mutagenicity was employed with use of Salmonella typhimurium strain TA 1535. Rats and hamsters were pretreated with 3-methylcholanthrene (MC), phenobarbital (PB) or Aroclor 1254 (AR). In the rat most active post-mitochondrial supernatant preparations were obtained with PB and AR while in hamsters AR was most effective in increasing mutagenicity of NPYR. The influence of the various modifiers of mixed function oxidase activity on protein content was determined on liver subfractions. In the rat, no difference was observed in the protein content of post-mitochondrial or post-microsomal supernatant while all the inducers increased these parameters in the hamster. The same pretreatments were tested on the rate of microsomal alpha-hydroxylation of NPYR. In the rat, only AR pretreatment resulted in significant enhancement, while MC slightly decreased the rate. In the hamster, both MC and AR pretreatment markedly increased the rate. When NPYR alpha-hydroxylase is expressed per g of wet wt of liver, differences in the amount of microsomal protein are included and better agreement between metabolism and mutagenicity in PB pretreated animals is obtained. MC and AR pretreatment increased aldehyde dehydrogenase activity in post microsomal supernatants in both rats and hamsters, while PB only increased the activity in hamster preparations. (26 Refs)

63. METABOLISM AND MUTAGENIC ACTIVATION OF 2-ACETYLAMINOFLUORENE BY HUMAN LIVER AND LUNG.

Boobis AR, Brodie MJ, McManus ME, Staiano N, Thorgeirsson SS, Davies DS
Dept. Clinical Pharmacology, Royal Postgraduate Medical Sch., London, England
Adv Exp Med Biol; 136(partB):1193-1201 1982

Ability of microsomal fractions of human liver to metabolize 2-acetylaminofluorene (2-AAF) and the capacity of subcellular fractions of human liver and lung to convert 2-AAF and N-hydroxy-2-acetylaminofluorene (N-OHAAF) to mutagens were investigated. Microsomal fractions of human liver were relatively active in metabolizing 2-AAF, total oxidative metabolism being greater than that of male Sprague-Dawley rats. Rank order of activities with human liver was 7-hydroxylation greater than 3-hydroxylation greater than 9-hydroxylation greater than 5-hydroxylation. Thus, man is much more active at N- and 3-hydroxylation of 2-AAF than either rat or Rhesus monkey. In biopsies with preserved hepatic architecture, cigarette smoking was associated with significant increases in arylhydrocarbon hydroxylase (AHH) and 2-acetylaminofluorene 3-hydroxylase (2-AAF-3H) activities but not with any significant change in the other 2-AAF hydroxylases or in total cytochrome P-450 content. The correlation between 2-AAF-3H and AHH was significant (0.778) but both enzyme activities were increased in cigarette smokers. When the correlation coefficient was calculated for the non-smokers it was 0.532. The correlation between 2-acetylaminofluorene 7-hydroxylase and AHH was relatively poor (0.668) but only AHH activity was increased in cigarette smokers. No significant correlation between 2-acetylaminofluorene N-hydroxylase and AHH activities (0.554) could be seen. In non-smokers the correlation coefficient was only 0.452. Human liver microsomal fraction activated both 2-AAF and N-OHAAF into a mutagen, whereas human lung post-mitochondrial fraction activated only N-OHAAF into a mutagen. Considerable inter-individual variation in the ability of human tissue samples to activate 2-AAF into a mutagen was observed. The ability of microsomal fractions of human liver to activate 2-AAF to a mutagen did not correlate with N-hydroxylase activity nor with any other enzyme activity measured. Mutagenic activation of 2-AAF and N-OHAAF was unaffected by cigarette smoking. (16 Refs)

64. OPTIMUM S9 CONCENTRATIONS IN BACTERIAL MUTAGENICITY ASSAYS.

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Adv Exp Med Biol: 136(partB):1263-1269 1982

Activation of 2-acetylaminofluorene (AAF) in two assay systems using bacterial mutagenesis is discussed. A modified incubation mixture was prepared, containing soft agar, which was dispensed to either Ames test (AT) plates or fluctuation test (FT) replicate tubes. Results indicate that the soft agar and temperature change cause some loss of activity and have a slight effect on the S9 optimum compared with a conventional FT. The S9 optimum of the modified FT could be compared with the response in a conventional FT. The S9 optimum is altered in the modified test and resembles a characteristic AT response. The same result was obtained when purified microsomes were used for activation instead of S9-mix indicating that the diffusion of cytosolic constituents of S9 fraction is not responsible for the difference. The concentrations of NADPH and NADPH generating system do not influence the S9 optimum. The diffusing factor was investigated by the addition of a number of agents to FT incubate. The presence of corn oil increased and broadened the S9 optimum suggesting that the agent is lipophilic. The addition of DNA (57 ug/ml), protein (2.5 mg/ml bovine serum albumin), or glutathione (2.5 mg/ml), and uridine diphosphate glucuronic acid (250 ug/ml) did not affect the S9 optimum. The effects of two ring hydroxylated AAF metabolites on the activation of AAF were examined in an AT. While the 1-OH metabolite had a slight inhibitory effect on AAF activation, the 7-hydroxy metabolite had a stimulatory effect on AAF activation. Results suggest that feedback effects of relatively unreactive metabolite of AAF may offer a mechanism for the apparent diffusible inhibition of microsomal activation but if so the action of the metabolite must be complex. (4 Refs)

65. PARTICIPATION OF THE MICROSOMAL ELECTRON TRANSPORT SYSTEM IN MUTAGENIC ACTIVATION OF 4-DIMETHYLAMINOAZOBENEZENE, 4-METHYLAMINOAZOBENZENE AND THEIR 3'-METHYL-DERIVATIVES.

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Biochem Biophys Res Commun; 106(1):164-169 1982

An antibody to NADPH-cytochrome P-450 reductase inhibited the mutagenic effect (measured by the Ames' assay) of 4-dimethylaminoazobenzene, 4-methylaminoazobenzene, and their 3'-methyl derivatives by 90%. The antibody against the 3-methylcholanthrene-inducible major P-450 (MC-P-448) inhibited the mutagenicity of these four compounds by 90% while the antibody against the phenobarbital-inducible major P-450 inhibited the mutagenicity by 20%. These results indicate that the microsomal electron transport system, in particular MC-P-448, is involved in the mutagenic activation of carcinogenic amino azo dyes. (28 Refs)

66. ROLE OF GLUTATHIONE IN LIVER-MEDIATED MUTAGENICITY OF ACRYLONITRILE.

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Toxicol Lett; 11(3/4):305-311 1982

The mutagenic activity of acrylonitrile (ACN) was studied in Salmonella typhimurium strain TA 1530 after exposure to microsomes, cytosolic fractions and postmitochondrial fractions from untreated and phenobarbitone pretreated rats and mice. Glutathione (GSH), important in biotransformation of ACN, when added to the activation system, increased the mutagenic response. The adduct between ACN and GSH was not mutagenic. (25 Refs)

67. METABOLIC ASPECTS OF THE COMUTAGENIC ACTION OF NORHARMAN.

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Adv Exp Med Biol; 136(partB):1011-1025 1982

Microbial mutagenicity tests were conducted using norharman (beta-carboline) in the Ames Salmonella typhimurium assay with strain TA 98. Comutagenicity of norharman with aniline was demonstrated, and linear dose-response curves were obtained with the aniline metabolites phenylhydroxylamine and nitrosobenzene in the presence of 200 ug norharman.

Norharman was comutagenic with o-toluidine, but not with m- or p-toluidines. It induced mutagenesis in yellow OB dye, but not red dye number 2, which does not yield either aniline or o-toluidine upon hydrolysis. 3-Aminopyridine and 2-amino-3-methyl-pyridine were mutagenic in the presence of norharman, but eight other aminopyridine derivatives were not. Diphenylnitrosamine (DPhN) and diphenylamine (DPhA) were mutagenic in the presence of norharman and S-9 mix, but not without both added components in the incubation medium. Mutagenicity of DPhN seems to be due to DPhA formed metabolically. Other strains of S typhimurium (TA 1538, TA 1978) showed sensitivity to aniline + norharman, and strains TA 100 and TA 1535 were totally unaffected. A mixture of microsomes + supernatant + NADPH yielded more revertants than microsomes alone, microsomes + NADPH, or supernatant + NADPH. (41 Refs)

68. METABOLISM OF MUTAGENIC AMINO-GAMMA-CARBOLINES IN TRYPTOPHAN PYROLYSATES.

Kato R, Yamazoe Y, Ishii K, Mita S, Kamataki T, Sugimura T
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Adv Exp Med Biol; 136(partB):997-1009 1982

Metabolic activation of 3-amino-1,4-dimethyl-5H-pyrido[4,3-b]indole (Trp-P-1) and 3-amino-l-methyl-5H-pyrido[4,3-b]indole (trp-P-2) by hepatic microsomes and reconstituted cytochrome P-450 systems and characterization of the mutagenic intermediate are described. The mutagenic metabolite of Trp-P-2 was shown to be a 3-hydroxyamine derivative. Studies of change in mutagenicity of Trp-P-1 and Trp-P-2 in the Salmonella typhimurium TA 98 assay after treatment of microsome donor rats with polychlorinated biphenyl, 3-methylcholanthrene, and phenobarbital suggested that the activated form of the indole compounds and the N-hydroxylation of Trp-P-2 were catalyzed by cytochrome P-448. Metabolic activation of Trp-P-1 and Trp-P-2 by NADPH-cytochrome P-450 reductase, cytochrome P-448, and NADPH was demonstrated. Genetic differences in formation of Trp-P-2 in mice, species differences in induction of benzo(a)pyrene hydroxylase and Trp-P-2 N-hydroxylase between rabbits and rats, and mutagenic activation by human liver microsomes were also shown. N-hydroxy-Trp-P-2, probably the free radical derivative, is probably an ultimate mutagen, but further metabolic activations by enzymes in the supernatant fraction and in S typhimurium TA 98 cannot be excluded. (20 Refs)

69. IN VITRO MUTAGENIC ACTIVITY OF 5-(3,3-DIMETHYL-1-TRIAZENO)-IMIDAZOLE-4-CARBOXAMIDE (DTIC) IN EUKARYOTIC AND PROKARYOTIC CELLS.

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Carcinogenesis; 3(5):467-471 1982

The in vitro mutagenic activity of 5-(3,3-dimethyl-1-triazeno)-imidazole-4-carboxamide (DTIC), has been studied in bacteria and Chinese hamster cells with and without metabolic activation by rat liver microsomes. DTIC was found to be highly mutagenic in the two systems. It is noteworthy that DTIC in the prokaryotic systems did not require metabolic activation to be effective. By comparing the mutagenic activity on bacteria of DTIC and of its monomethyl- and hydroxymethyl-derivatives (MIC and HMIC), it is evident that MIC and HMIC display a pattern of mutagenicity different from DTIC. It suggests that neither MIC nor HMIC are the direct responsible metabolites for the mutagenic activity of DTIC in bacteria. (Author abstract) (34 Refs)

70. GENOTOXICITY EVALUATION OF AMSACRINE (MEETING ABSTRACT)

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Department of Toxicology, Warner-Lambert/Parke-Davis Research Division, Ann Arbor, MI, 48105
Toxicologist; 2(1):175 1982

Acridinylamino derivatives constitute compounds with antineoplastic properties. Comparative genotoxicity and hence carcinogenic potential of 4'-(9-acridinylamino) methanesulphon-m-anisidide (amsacrine) was studied in several bacterial and mammalian cell in vitro assays. In a Salmonella plate incorporation assay, reverse mutation was observed only at 269 ug/plate in the nonactivation phase in frameshift tester strain TA-1537. In a preincubation modification of this assay, significantly increased revertant counts were obtained in TA-1537, TA-1535, and TA-100 at a cytotoxic dose of 672 ug/plate without S9. In the presence of S9, mutagenic activity was manifest only with TA-1537, indicating that potential base substitution activity of amsacrine was prevented more readily than its frameshift activity specific for TA-1537. At these high cytotoxic doses, a significant portion of presumed revertants did not grow in histidine-deficient medium and could have represented phenocopies. By contrast, doses as low as 0.02 ug/ml in culture medium without S9 induced a greater than five-fold increase in sister-chromatid exchange (SCE) rate and chromosomal damage frequency in Chinese hamster ovary cells in vitro. SCE response was more sensitive to S9 detoxification than the chromosomal aberration frequency. (no Refs)

71. INVESTIGATIONS ON THE MUTAGENIC AND CLASTOGENIC ACTIVITY OF RESORCIN. CYTOGENETIC FINDINGS FROM DIFFERENT TYPES OF HUMAN CELLS.

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Arzneim Forsch; 32(5):533-536 1982

The suspected clastogenic effect of m-dihydroxybenzene (resorcin), a phenol derivate, was investigated by analyzing three different types of human cells: (1) lymphocyte cultures from blood of healthy blood donors with normal karyotype (46, XY); (2) lymphocyte cultures from patients with a proven chromosome abnormality (trisomy 21, karyotype: 47, +21); and (3) cultures of amniotic cells with normal karyotype (46,XX and 46,XY). In all three cell systems resorcin induces secondary chromosome aberrations. The number of cells with aberrations increases with the concentration of the substance and duration of action. The three cell systems tested showed a different sensibility to resorcin. Lymphocytes with trisomy 21 were more sensitive than the same cell type with a normal karyotype. Both types of lymphocytes were less sensitive to resorcin than amniotic cells. The types of structural chromosome aberrations observed in these investigations as well as the concentration of the test substance, which had to be added to induce a clastogenic effect, demonstrated that resorcin has to be regarded as a weak mutagenic substance. (Author abstract) (16 Refs) (In GER)

72. MUTAGENICITY OF TRANS-ANETHOLE, ESTRAGOLE, EUGENOL, AND SAFROLE IN THE AMES SALMONELLA TYPHIMURIUM ASSAY.

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Bull Environ Contam Toxicol; 28(6):647-654 1982

The mutagenic activities of safrole, anethole, and eugenol in Salmonella typhimurium were investigated using the Ames method as well as the effect of incorporation of 3'-phosphoadenosine 5'-phosphosulfate (PAPS). The increase of revertant colonies as a result of incorporating PAPS into the microsomal, but not into the direct bacterial assay, suggested that safrole and related compounds may be converted to DNA binding sulfuric acid esters under the applied conditions. Incorporation of proper cofactors and soluble enzymes in vitro mutagenicity screens was important for optimization of the mutagenic response. (17 Refs)

73. STRUCTURE-ACTIVITY STUDIES ON THE MUTAGENICITY OF TRIS(2,3-DIBROMOPROPYL)PHOSPHATE (TRIS-BP) AND ITS METABOLITES IN SALMONELLA.

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Environ Mutagen; 4(3):271-277 1982

Five methylated metabolites of the flame retardant tris(2,3-dibromopropyl)phosphate (Tris-BP) were tested for mutagenicity in Salmonella typhimurium strains TA1535 and TA100. The metabolites tested produced a gradient of mutagenic responses in TA1535 in the same dose range and up to the same magnitude as the Tris-BP response. None appeared to be the ultimate mutagen, since all required the S-9 fraction. The loss of the first dibromopropyl group did not affect mutagenicity whereas loss of the next dibromopropyl group resulted in decreased mutagenicity. The loss of bromine and the addition of a double bond between carbons 2 and 3 further decreased mutagenicity. Trimethyl phosphate was mutagenic in strain TA100 both in the presence and absence of S-9. Tripropyl phosphate was not mutagenic at any of the doses tests in TA100 or TA1535, with or without S-9. A possible detoxification pathway for these compounds is discussed. (12 Refs)

74. MICROBIOLOGICALLY-MEDIATED MUTAGENIC ACTIVITY OF CRUDE OIL. FINAL REPORT, 1976-1979.

Cummings BA, Gordon RC
Dept. Microbiology, Colorado State Univ., Fort Collins, CO
Sci Tech Aerosp Rep; 20(7):957-958 1982

Crude oil was incubated with raw and sterile river water samples and assayed for mutagenic activity for the Ames test to determine the ability of naturally occurring freshwater microorganisms to form mutagenic biodegradation products from crude oil. River water samples supplements with inorganic salts were incubated with one percent crude oil in Erlenmeyer flasks for 1-6 wk and 4 and 20 C with shaking. Replicate flasks were extracted at various time intervals with 1,1-2 trichloro-1,2,2-trifluoroethane, the solvent evaporated with the residues taken up in dimethyl sulfoxide for mutagenicity testing. The extracts were assayed for mutagenic activity by the plate incorporation methods of the Ames test with Salmonella tester strains TA 100, TA 1535, TA 1537, TA 1538 and TA 98. Mammalian liver microsomes were not used in the mutagenicity test system as the oil degrading microorganisms constituted the enzyme activation system in the study. (Author abstract)

BINDING OF CARCINOGENS AND THEIR METABOLITES TO MACROMOLECULES

75. COVALENT BINDING OF METABOLICALLY ACTIVATED HYDROCARBONS TO SPECIFIC MICROSOMAL PROTEINS.

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Adv Exp Med Biol; 136(partA):341-348 1982

Binding specificity of benzene (BZ), chlorobenzene (CB), 3-methylcholanthrene (MCH), and benzo(a)pyrene (BP) to rat liver microsomal proteins (MP) after metabolic activation was examined. The examined compounds bound covalently to MP in a NADPH-dependent manner indicating that metabolic activation was required for binding. Reduced glutathione inhibited binding. The binding patterns to MP examined by SDS-polyacrylamide gel electrophoresis and fluorography were quite similar for metabolic activated BZ, CB, and phenol. The binding patterns to liver microsomes from phenobarbital (PB)- or MCH-treated rats did not differ significantly from those of control animals. The binding patterns for BP and MCH were distinctly different from those of BZ, phenol, and CB. The binding of these compounds to microsomes from MCH-treated rats was much higher than that to microsomes from control or PB-treated animals. Seven BP metabolites were isolated and incubated with NADPH and microsomes from control or pretreated rats. All isolated metabolites, including BP-4,5-oxide, had to be metabolically activated to bind covalently. Variations were found among the metabolites in extent and specificity of binding. Of the isolated metabolites tested, BP-7,8-dihydrodiol bound most efficiently after metabolic activation, particularly to microsomes from MCH-treated rats. Results suggested that the binding pattern, at least in part, is determined by the mechanism of metabolic activation. (13 Refs)

76. INTERACTION OF BENZO(A)PYRENE AND ITS DIHYDRODIOL-EPOXIDE DERIVATIVE WITH NUCLEAR AD MITOCHONDRIAL DNA IN C3H10T1/2 CELL CULTURES.

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Cancer Res; 42(7):2764-2769 1982

To analyze the distribution of radioactive carcinogens and [3H]thymidine between nuclear DNA (nDNA) and mitochondrial DNA (mtDNA), we have developed a simple and rapid method for the separation of nDNA and mtDNA using gel electrophoresis of cell lysates. Using this method, we found that, when C3H10T1/2 cells are exposed to either 0.5 uM [3H]-(+-)-7beta,8alpha-dihydroxy-9alpha,10alpha-epoxy 7,8,9,10-tetrahydrobenzo(a)pyrene ([3H]BPDE) or 1 uM [3H]benzo(a)pyrene, the mtDNA contains a major fraction of the total adducts formed with cellular DNAs. Deoxynucleoside adducts formed between benzo(a)pyrene and mtDNA in intact C3H10T1/2 cells or between BPDE and isolated rat liver mtDNA were analyzed by high-performance liquid chromatography, and were found to be much more heterogeneous than those present in nDNA of C3H10T1/2 cells. The extensive modification of mtDNA with BPDE in C3H10T1/2 cells is associated with preferential inhibition of the incorporation of [3H]thymidine into mtDNA when compared to incorporation of [3H]thymidine into nDNA. To analyze the factors responsible for the extensive modification of mtDNA by BPDE, we investigated the role of a lipid phase utilizing liposome:DNA complexes as a model system. We found that the liposomes protect BPDE from spontaneous hydrolysis and enhance the extent of DNA modification at low DNA concentrations. These findings extend previous evidence suggesting that the mitochondria may be important cellular targets in the process of chemical carcinogenesis. (Author abstract) (29 Refs)

77. BENZO[A]PYRENE AND OTHER INDUCERS OF CYTOCHROME P1-450 INHIBIT BINDING OF EPIDERMAL GROWTH FACTOR TO CELL SURFACE RECEPTORS.

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Carcinogenesis; 3(5):505-510 1982

The binding of 125I-labeled epidermal growth factor (EGF) was utilized to monitor possible cell surface effects of polycyclic aromatic hydrocarbon carcinogens. Exposure of confluent C3H 10T1/2 mouse fibroblasts to 1 uM benzo[a]pyrene led to a time-dependent decrease of EGF binding. By 24 hr, EGF binding was only 5% that of control cultures. In contrast, benzo[a]pyrene-7,8-diol-9,10-oxide did not significantly alter EGF binding, indicating that the inhibition by benzo[a]pyrene was not simply due to DNA damage. A curvilinear Scatchard plot in the control cells was consistent with the presence of two classes of EGF receptors having differing affinities. Our results suggest that the major effect of benzo[a]pyrene was a reduction in receptor number rather than affinity, although other interpretations have not been excluded. Progesterone, 17beta-estradiol, benzo[e]pyrene, cholesterol, phenobarbital, 1,1-bis-(p-chlorophenyl)-2,2,2-trichloroethane, hexachlorobenzene or pregnenolone-16alpha carbonitrile, did not inhibit EGF binding. On the other hand, several known inducers of P1-450 were very effective inhibitors of EGF binding. These included: dimethylbenz[a]anthracene, 3-methylcholanthrene, benzo[a]pyrene, benz[a]anthracene, beta-naphthoflavone and alpha-naphthoflavone. We postulate that the binding of certain polycyclic aromatic hydrocarbons to the Ah receptor may induce not only specific drug metabolizing enzymes but also inhibition of EGF binding, and possible other cell effects. Further studies are required to verify this hypothesis. (Author abstract) (41 Refs)

78. MODULATION OF EPOXIDE HYDROLASE ACTIVITY. EFFECT ON THE ACTIVATION OF BENZO[A]PYRENE AND ITS COVALENT BINDING TO DNA IN THE NUCLEUS.

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Adv Exp Med Biol; 136(partA):705-716 1982

Role of epoxide hydrolase (EH) in binding 7,8-dihydrodiol-9,10-oxide (DDO) and 9-hydroxy-benzo(a)pyrene-4,5-oxide (HBPO) to DNA was investigated using isolated rat liver nuclei. EH levels were moderated using trans-stilbene oxide (TSO) and trichlorpropilene oxide (TCPO). Male Sprague-Dawley rats were treated with 3-methylcholanthrene (MC) and/or TSO. Patterns of modified nucleosides obtained from incubation of nuclei with 3H-benzo(a)pyrene (BP) are presented. When purified EH in 10-fold excess of the amount present in the nuclei was added to the incubation medium the degree of HBPO binding was diminished in the controls. Similar results were obtained when nuclei from MC plus TSO-treated rats were used. Results of experiments using nuclei and 7.5 mg of microsomal protein from MC-treated rats were very similar to those obtained using nuclei alone, except that the total binding of both BP metabolites was higher. The amount of HBPO binding was lower when the EH activity was increased, but binding of DDO was not changed. When EH was inhibited by TCPO, DDO binding decreased and HBPO increased. Individual pathways of BP metabolism are presented. Results showed that the levels of EH activity greatly influence the amounts and patterns of BP-derived metabolites binding to DNA, and imply that EH activity is an important factor in influencing the in vivo carcinogenicity of BP and other polycyclic hydrocarbons. (35 Refs)

79. METABOLISM OF BENZO(A)PYRENE BY HUMAN EPITHELIAL AND FIBROBLASTIC CELLS: METABOLITE PATTERNS AND DNA ADDUCT FORMATION.

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J Cell Biochem; 18(2):135-148 1982

The metabolism of benzo(a)pyrene (BaP) and DNA adduct formation were compared in the same incubations of mammary epithelial cells grown out in early passage, from each of three human subjects, and of fibroblasts from one of these subjects. Mammary epithelial cells showed the preferential formation of 7,8-dihydrodiol-9,10-dihydroepoxybenzo(a)pyrene, (BPDE) the ultimate carcinogen. The end products of BaP metabolism in fibroblasts, unlike epithelial cells, were mainly mono- and dihydroxide derivatives of BaP. The greater ease of DNA adduct formation in epithelial cells is apparently related to the metabolites produced from BaP by these cells. The metabolite results indicate that mammary epithelial cells preferably converted BaP to diols, some of which were conjugated with glutathione at the first epoxidation step. The remaining dihydrodiols were readily converted to BPDE, a large portion of which ended up as tetrols and glutathione conjugates, but in the process BPDE was available to react with DNA. The accumulation of diols in the later stages of fibroblast incubations indicates that these cells have a much lower capacity to convert diols to the diolepoxide than do mammary epithelial cells. These results support the theory that chemical carcinogens may be involved in the induction of human breast cancer. (46 Refs)

80. MECHANISM OF ORGAN-SPECIFIC TUMOR INDUCTION IN THE GASTRO-INTESTINAL TRACT (MEETING ABSTRACT)

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J Cancer Res Clin Oncol; 103(Suppl):A11 1982

The metabolism and reaction with DNA of three carcinogens was investigated after systemic administration selectively induced tumors in different segments of the gastro-intestinal tract. These agents share a common ultimate carcinogen, methyl diazonium ion, and produce an identical pattern of methylated DNA bases. Following oral or systemic administration in rats, N-nitrosomethylbenzylamine (MBN) induced a high incidence of esophageal carcinomas. Methylation of DNA purines by a single iv dose of (methyl-14C) MBN is most extensive in the esophagus, followed by liver, lung and forestromach. In mice, systemic application of MBN resulted in the development of forestomach carcinomas as in this species, DNA methylation by MBN is higher in forestomach than in esophageal DNA. The alternative possibility of enzymic hydroxylation of the methyl group of MBN cannot be ruled out but after administration of (methylene-14C) MBN no benzylated DNA bases were detected in rat tissues. Methyl(acetoxymethyl)nitrosamine (DMN-OAc) is a stable derivative of the alpha-hydroxy intermediate of dimethylnitrosamine. Heterolytic decomposition of DMN-OAc occurs through esterase mediated cleavage of the acetoxy moiety. Following iv injection of (14C)DMN-OAc by far the highest levels of DNA alkylation were found in the lung, the principal target organ for this route of application. In contrast, ip injection of (14C) CMN-OAc resulted with a preferential alkylation of organs bordering the abdominal cavity with highest values in ileum and colon, the target organs for this route of application. Weekly sc injection of 1,2-dimethylhydrazine (DMH) in rats and mice cause a selective induction of colon carcinomas. Alkylation of DNA purines by DMH was highest in liver, followed by colon, kidney and ileum. (no Refs)

81. REACTIVE INTERMEDIATES FROM NITROSAMINES.

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Adv Exp Med Biol; 136(partB):1027-1035 1982

Experiments with reactive intermediates from nitrosamines are reviewed. Rat liver fractions prepared from homogenate were incubated with 0.28 mole of N-nitrosodi-n-propylamine (NDPA) at 37 C. Microsomal metabolism of NDPA in vitro led to production of isopropanol and n-propanol through the intermediary of a carbocation. DNA obtained from livers of Sprague-Dawley rats previously injected ip with N-[2,3(3)-H]nitrosodi-n-propylamine was incubated with 7-n-propylguanine (7-nPG) and 7-isopropylguanine (7-iPG) and then hydrolyzed. Reverse phase chromatography showed that the DNA hydrolysate contained 7-nPG only, although a similar experiment demonstrated 7-iPG in rat liver RNA. N-nitroso-2-hydroxypropylpropylamine (NHPPA) was also isolated from the in vitro reaction mixture following incubation of NDPA with the microsomal fraction of rat liver. NHPPA could be oxidized further to form N-nitroso-2-oxopropylpropylamine (NOPPA). Administration of highly purified NOPPA to rats leads to formation of O(6)-methylguanine and 7-methylguanine in the ratio or 0.07. This ratio of the two methylated guanines is similar to that obtained following administration of N-nitrosodimethylamine (NDMA) at comparable dose levels, suggesting that the methylating agent formed from NOPPA is similar in reactivity to that formed from NDMA, and supporting the hypothesis that N-nitrosomethylpropylamine may be the methylating agent formed from NOPPA. (23 Refs)

82. INTERACTION OF REACTIVE INTERMEDIATES WITH DNA.

Magee PN, Chu CK, Gombar CT, Jensen DE, Parchman LG
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Adv Exp Med Biol; 136(partB):1335-1347 1982

Covalent binding of some selected chemicals to rat liver DNA is described and the results related to the proposal by Lutz that the extent of binding may be a quantitative indicator in the process of chemical carcinogenesis. Lutz suggested that covalent binding may be expressed in quantitative terms as the Covalent Binding Index relating damage to DNA as a function of dose. N-nitrosodimethylamine was used as a positive control. No in vivo interaction of N-nitrosoproline with rat liver DNA was observed. Since this compound was rapidly eliminated from the body and a very small degree of metabolism occurred, the use of proline as a safe test compound in studies on endogenous nitrosation is supported in animals and humans. A very small, but real interaction between trichloroethylene and mouse liver DNA in vivo was observed, supporting the apparent low carcinogenic potency of the compound and doubts concerning its carcinogenicity. In the presence of sulfhydryl compounds, N-nitrosocimetidine interacted with calf thymus DNA in vitro, yielding a pattern of methylated purine bases identical to that produced by N-methyl-N'-nitro-N-nitrosoguanidine (MNG) and other carcinogenic and mutagenic N-nitroso compounds. Preliminary in vivo experiments indicated that the extent of methylation of DNA was much less in organs of animals treated with nitrosocimetidine than those treated with MNG. (37 Refs)

83. N-PROPYLDIAZONIUM ION ALKYLATES O6 OF GUANINE WITH REARRANGEMENT, BUT ALKYLATES N7 WITHOUT REARRANGEMENT.

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Cancer Lett; 16(1):51-56 1982

The product distribution obtained from the reaction of guanine with the n-propyldiazonium ion was investigated. In both in vitro experiments using guanosine and in vivo experiments in which male Sprague-Dawley rats received an injection of 0.3 millimole 3H-di-n-propylnitrosoamine and RNA extracted 12 hr later, alkylation of 7 position of guanine proceeded primarily without rearrangement. Because of the ready rearrangement of the presumed n-propyl cation to the isopropyl cation, alkylation products of n-propylnitrosourea should have been isopropyl derivatives. Most O6-alkylation products were the result of n-propyl cation rearrangement, ie, O6-isopropylguanosine. These results suggest that a new view of alkylation in aqueous media must be developed, and that classical approaches for describing reactivity of alkylating agents are inadequate. (10 Refs)

84. FORMATION OF 7-METHYLGUANINE IN LIVER DNA FROM RATS TREATED IN VIVO WITH N-NITROSOPYRROLIDINE (MEETING ABSTRACT)

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Toxicologist; 2(1):182 1982

It is known that 7-methylguanine (7-MG) is formed in liver DNA during hepatotoxicity induced by a variety of chemicals that cannot directly methylate DNA. In a study using radiolabeled N-nitrosopyrrolidine (NP), it was shown this hepatotoxin and hepatocarcinogen is not metabolized in the rat to an agent which methylates liver DNA guanine. 7-MG was detected in liver DNA of adult male Sprague-Dawley rats after administration of a hepatotoxic dose of NP using a highly sensitive high pressure liquid chromatography method which optically detects fluorescent alkylated purines in DNA hydrolysates without the need for radiolabel. Rats were given 14, 28, 57, 113, 225, 450, or 900 mg NP/kg body wt and decapitated 12 hr later; liver DNA was isolated, purified, and hydrolyzed at pH 7.0 or 1.0. The amount of 7-MG in liver DNA obtained at each dose level was 25, 64, 87, 58, 97, 112, 57 u mol per mol guanine, respectively. The detection of 7-MG in liver DNA of rats treated with NP is consistent with similar observations in liver DNA from rats treated with such diverse hepatotoxins as hydrazine, carbon tetrachloride, ethanol, phosphorus, bromobenzene, and puromycin. (2 Refs)

85. MEASUREMENTS BY FILTER ELUTION OF DNA SINGLE- AND DOUBLE-STRAND BREAKS IN RAT HEPATOCYTES: EFFECTS OF NITROSAMINES AND GAMMA-IRRADIATION.

Bradley MO, Dysart G, Fitzsimmons K, Harbach P, Lewin J, Wolf G
Merck Inst. Therapeutic Res., West Point, PA, 19486
Cancer Res; 42(7):2592-2597 1982

This work presents a filter elution method for measuring DNA single- and double-strand breaks in primary rat hepatocytes without radioactive labeling of DNA. We have studied the effects of a series of nitrosamines and of gamma-irradiation on DNA single- and double-strand break induction. The repair of DNA single-strand breaks in the hepatocytes was measured after treatment with 60Co, 1-methyl-1-nitrosourea, and N-nitrosodimethylamine. The hepatocytes were isolated by ethylene glycol-bis(beta-aminoethyl ether)-N,N'-tetra acetic acid-collagenase perfusion and had a mean viability of 91 +-4% (SD). The isolated cells were treated for varying lengths of time with nitrosamines in suspension culture in L-15 medium containing 10% fetal bovine serum. After treatment, the cells were chilled, loaded onto 2-um polycarbonate filters, and lysed in a 2% sodium dodecyl sulfate-proteinase K solution, pH 9.6. The DNA was eluted from the filter at either native or denaturing pH with fractions collected every 3 hr. The quantity of DNA in each fraction was determined by measuring the fluorescent product formed between it and diaminobenzoic acid after ethanol-sodium acetate precipitation and trapping of the DNA on 0.2-um polycarbonate filters. The results show that the carcinogens, N-nitrosodimethylamine, N-nitrosodiethylamine, N-nitrosodipropylamine, N-nitrosodibutylamine, and 1-nitrosopiperidine all made dose- and time-related increases in the number of single-strand breaks in rat hepatocytes. N-Nitrosodiphenylamine produced small numbers of single-strand breaks. No double-strand breaks were formed by any of the nitrosamines. Single-strand breaks induced by N-nitrosodimethylamine were repaired very slowly relative to repair of either gamma-ray or 1-methyl-1-nitrosourea-induced single-strand breaks. This system has many advantages for studying carcinogen metabolism and DNA damage in hepatocytes, one of the major target cells for many carcinogens. (Author abstract) (19 Refs)

86. QUANTITATIVE ASSESSMENT OF CARCINOGEN-MODIFIED DNA IN SPECIFIC LIVER CELL POPULATIONS FOLLOWING A SINGLE DOSE N-2-ACETYLAMINOFLUORENE (AAF) OR ITS N-HYDROXY DERIVATIVE (N-OH-AAF) (MEETING ABSTRACT)

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Toxicologist; 2(1):103 1982

AAF-induced hepatocarcinogenesis appears to be targeted to parenchymal cells (PC). Our objective was to determine whether or not there is preferential binding of carcinogen (C) residues to the DNA of these target cells and, if so, the possible basis for the selectivity. AAF and its N-hydroxy derivative (N-hydroxyl-N-2-acetylaminofluorene), the first product in the metabolic activation of AAF, were employed for these studies. Male Sprague-Dawley rats weighing 200-250 g were injected, ip, with (ring-3H)AAF or (ring3H)-N-OH-AAF. Animals were sacrificed at either the time of peak binding of C to DNA, 2 hr or 18 post-injection, when N-OH-AAF or AAF, respectively, were used, and at 3 days after maximum binding. PC and nonparenchymal (NPC) cells were isolated by centrifugal elutriation. Following AAF administration, the u moles of adducts formed/mg DNA of PC was 2.7 times that of the NPC. When N-OH-AAF was employed, equal amounts of adducts were found associated with DNA of PC and NPC. By 3 days after the period of maximum DNA binding 50-59% of the adducts initially present remained in the DNA of both cell types following administration of either AAF or N-OH-AAF. These results suggest that AAF preferentially damages DNA of PC due to an increased capacity of these cells to carry out the N-hydroxylation of AAF. (no Refs)

87. METABOLISM AND NUCLEIC ACID BINDING OF 7-FLUORO-2-ACETAMIDOFLUORENE IN RATS: OXIDATIVE DEFLUORINATION AND APPARENT DISSOCIATION FROM HEPATOCARCINOGENESIS OF 8-(N-ARYLAMIDE)GUANINE ADDUCTS ON DNA.

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Chem Biol Interact; 40(1):27-43 1982

The significance in hepatocarcinogenesis of various arylamine/amide adducts with nucleic acid was investigated. Female Fischer and Sprague Dawley rats are comparably sensitive to hepatocarcinogenesis by 2-acetamidofluorene (AAF), while male rats are more sensitive. 7-Fluoro-2-acetamidofluorene is more carcinogenic in Sprague-Dawley rats than is AAF, and strikingly so toward the liver of female rats. Binding of both compounds to liver nucleic acids was determined for Fischer rats at 1 and 3 days after a single injection of carcinogen, and in female Sprague-Dawley rats from 1 to 28 days after a single injection. No 8-(N-2-fluorenylacetamido)guanine adduct or the 7-fluoro derivative could be found in RNA or DNA of female Sprague-Dawley rats treated with AAF These adducts were present in comparable amounts in both male and female Fischer rats. The binding of 7-fluoro-AAF derivatives was higher than that of AAF derivatives in female Sprague-Dawley rats. Feeding of either AAF or 7-fluoro-AAF to Sprague-Dawley rats for 4 wk before a single injection of [3H]7-fluoro-AAF resulted in reduction of the 8-(N-2-(7-fluoro)fluorenyl-acetamido)guanine adduct in males to undetectable levels in DNA and to 10% of control level in RNA. Non-acetylated adducts were increased in males, but decreased in females by AAF prefeeding; 7-fluoro-AAF prefeeding resulted in little change in adduct formation in females and in a major increase in non-acetylated adducts in males. AAF adducts disappeared from DNA more rapidly than did 7-fluoro-AAF adducts. Assay of the urinary metabolites from the animals in the prefeeding experiment showed that all compounds fed increased the proportion of N-hydroxy-7-fluoro-AAF among the metabolites. Defluorination of 7-fluoro-AAF to 7-hydroxy-AAF was also demonstrated and the ratio of 7-hydroxy-AAF to 5-hydroxy-7-fluoro-AAF was comparable to that observed for 7-hydroxy-AAF/5-hydroxy-AAF and AAF itself, suggesting that fluoro substitution does not increase activity by preventing detoxication. (28 Refs)

88. CYTOCHROME P-450-AND FLAVIN-CONTAINING MONOOXYGENASE-CATALYZED FORMATION OF THE CARCINOGEN N-HYDROXY-2-AMINOFLUORENE AND ITS COVALENT BINDING TO NUCLEAR DNA.

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Cancer Res; 42(7):2671-2677 1982

The metabolic N-oxidation of the carcinogen 2-aminofluorene was examined in vitro using fortified hepatic microsomes from a variety of species. Rat, dog, human, and pig liver microsomes catalyzed the formation of N-hydroxy-2-aminofluorene (N-OH-AF) from AF at rates of 1.6, 1.0, 1.2, and 3.5 nmol/min/mg protein, respectively. The involvement of both cytochrome P-450 and the flavin-containing monooxygenase was demonstrated with hepatic microsomes and with purified enzymes by using specific enzyme inhibitors. 2-[(2,4-Dichloro-6-phenyl)phenoxy]ethylamine, a potent cytochrome P-450 inhibitor, decreased microsomal N-OH-AF formation by 96, 83, 70, and 46% in the rat, dog, human, and pig, respectively; and further addition of methimazole, a high-affinity flavin-containing monooxygenase substrate, abolished the residual N-hydroxylating activity. Using the purified porcine flavin-containing monooxygenase, metabolic formation of N-OH-AF occurred at a rate of 4.9 nmol/min/nmol flavin adenine dinucleotide and was insensitive to 2-[(2,4-dichloro-6-phenyl)phenoxy]ethylamine inhibition. In addition, purified rat liver cytochrome P-450 (isolated from 5,6-naphthoflavone-induced animals) N-hydroxylated AF (1.1 nmol/min/nmol P-450) and was completely inhibited by 2-[(2,4-dichloro-6-phenyl)-phenoxy]ethylamine, but the reaction was insensitive to methimazole. To determine whether or not the metabolic formation of N-OH-AF could lead directly to covalently bound adduct(s) with DNA under these incubation conditions (30 min, pH 7.5), the binding of synthetic and metabolically formed [3H]-N-OH-AF to added calf thymus DNA and to DNA in isolated rat liver nuclei was investigated. In all cases, the amount of DNA-bound carcinogen accounted for 0.08 to 0.15% of the N-OH-AF present in the incubation mixtures. These data, when compared to the levels of AF bound to hepatic nuclear DNA reported in vivo, suggest that the nonenzymatic reaction of N-OH-AF with nuclear DNA may be sufficient to account for a substantial portion of the observed in vivo binding of this carcinogen. (Author abstract) (77 Refs)

89. COVALENT BINDING OF BENZIDINE AND N-ACETYLBENZIDINE TO DNA AT THE C-8 ATOM OF DEOXYGUANOSINE IN VIVO AND IN VITRO.

Martin CN, Beland FA, Roth RW, Kadlubar FF
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Cancer Res; 42(7):2678-2686 1982

Benzidine, a human urinary bladder carcinogen, induces hepatic tumors in mice and rats. In this study [3H]benzidine was administered in drinking water to mice for 1 wk, and the covalent binding of the carcinogen to hepatic DNA was then determined. A single carcinogen: DNA adduct was detected which decreased in concentration by approx 50% at 1 day after treatment and then remained at a nearly constant level for at least 7 days. Injection of radiolabeled benzidine or N-acetylbenzidine into rats also resulted in a single carcinogen:DNA adduct that was chromatographically identical to that obtained in mouse liver. While administration of benzidine and N-acetylbenzidine resulted in high levels of the adduct in rat hepatic DNA, injection of N,N'-[ring-14C]diacetylbenzidine did not give detectable binding. The same carcinogen:DNA adduct found in rat and mouse liver was prepared synthetically by: (a) hydrolysis of calf thymus DNA reacted with N-hydroxy-N'-acetylbenzidine at pH 5; and (b) reaction of N-acetoxy-N,N'-diacetylbenzidine with deoxyguanosine and subsequent selective deacetylation of the product with methanolic ammonia. Mass and nuclear magnetic resonance spectral data of the synthetic products established the structure of the hepatic adduct as N-(deoxyguanosin-8-yl)-N'-acetylbenzidine. The nonacetylated derivative, N-(deoxyguanosin-8-yl)benzidine, was synthesized by carboxylesterase treatment of N-(deoxyguanosin-8-yl)-N'-acetylbenzidine and was shown not to occur in rat and mouse liver DNA. These data indicate that the metabolic activation of benzidine to an ultimate carcinogen in rats and mice does not involve N-hydroxybenzidine or sulfotransferase-catalyzed activation of N-hydroxy-N,N'-diacetylbenzidine. The remaining pathways for metabolic conversion of benzidine to an ultimate carcinogenic species are discussed in relation to liver and urinary bladder carcinogenesis. (46 Refs)

90. COMPARATIVE BIOCHEMISTRY AND METABOLISM. PART 1. CARCINOGENESIS. ANNUAL REPORT, JUN. 1980-MAY 1981.

Shank RC
Aerospace Medical Res. Lab., Wright-Patterson Air Force Base, Ohio
Sci Tech Aerosp Rep; 20(8):1128-1129 1982

Oral administration of the inorganic hepatotoxin, hydrazine, to male Fischer 344 or Sprague Dawley rats results in the endogenous methylation of liver DNA at the 7-and O6-positions of guanine. At doses below the LD50 (45, 60 or 75 mg hydrazine/kg body wt), methylation levels varied little and averaged about 500 micromol 7-methylguanine/mol guanine and 20 micromol O6-methylguanine/mol guanine. At 90 mg hydrazine/kg body wt (approx the 7-day LD50) the methylation levels were 869 micromol 7-methylguanine and 58 micromol O6-methylguanine/mol guanine 24 hr after toxicant administration. A single dose of 3 mg hydrazine/kg body wt did not result in detectable levels of methylguanines in liver DNA; however, after three or four daily administrations of hydrazine at this dose, liver damage was evident, and liver DNA contained 50-100 micromol 7-methylguanine/mol guanine, about the limit of analytical detection. Following a single oral administration of 90 mg hydrazine/kg body wt, liver DNA guanine rapidly became methylated. The time for half-maximum alkylation of 7-guanine was 30 minutes and at O6-guanine, 45 minutes. The rates of removal of these methylated bases were consistent with published values from experiments using methylating carcinogens and with values obtained in this laboratory with the model compound, 1,2-dimethylhydrazine. (Author abstract)

91. METABOLIC ACTIVATION OF ADRIAMYCIN BY NADPH-CYTOCHROME P-450 REDUCTASE, RAT LIVER AND HEART MICROSOMES AND COVALENT PROTEIN BINDING OF METABOLITES.

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Adv Exp Med Biol; 136(partA):471-485 1982

NADPH-dependent covalent binding of adriamycin-metabolites to bovine serum albumin and microsomal proteins in an aerobic in vitro-system with isolated NADPH-cytochrome P-450 reductase, rat liver, and rat heart microsomes, respectively, is reported. The covalent binding was revealed by means of spectrophotometric identification of the anthracycline moiety of the covalently bound adriamycin-metabolites. Based on this study and others, a model for the mechanism of antineoplastic, myelosuppressive, and cardiotoxic action of adriamycin, respectively, was proposed. Two reactive intermediates are generated in a cyclic process of bioreductive activation of adriamycin and spontaneous reoxidation; semiquinone radicals of adriamycin and superoxide radicals. NADPH and oxygen are consumed at the same time. Superoxide radicals formed by reoxidation and other reactive oxygen-species generated could be responsible for the destruction of intracellular macromolecules. The semiquinone radicals of adriamycin formed by bioreductive activation are metabolized to 7-deoxy-adriamycin-aglycone. The concomitant depletion of soluble sulfhydryls like glutathione may lead to further toxic effects. The results suggest covalent protein binding of adriamycin-semiquinone radicals formed by NADPH-cytochrome P-450 reductase. Because covalent protein binding also occurred in rat heart microsomes, this biological effect may contribute to adriamycin-induced cardiotoxicity; this method of determining covalent binding of adriamycin-metabolites to cardiac protein may be a useful in vitro test system for the analyzing the cardiotoxicity of new antineoplastic anthracycline antibiotics. (37 Refs)

92. ETHIONINE INHIBITS IN VIVO METHYLATION OF NUCLEAR PROTEINS.

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Carcinogenesis; 3(4):431-434 1982

Nuclear protein methylation was studied in regenerating rat liver by giving [methyl-3H]methionine 45 hr after partial hepatectomy. Ethionine, a liver carcinogen, has been shown to alter the methylation patterns in a basic protein (histone) fraction, as well as an acidic protein (non-histone) fraction present in a 0.25 N HCl nuclear extraction. The proteins present in the 0.25 N HCl extraction were separated by chromatography using Bio-Rex 70 cation exchange column. Polyacrylamide gel electrophoresis and total amino acid analysis showed the first protein fraction contained acidic large mol wt non-histone proteins, while the second fraction contained basic small mol wt histone proteins. Both fractions were then hydrolyzed, and the amino acids chromatographed on an Aminex A-5 cation exchange column. The histones were found to contain epsilon-N-mono, di and trimethyllysine derivatives; whereas the non-histone fraction contained these lysine derivatives and an additional basic amino acid identified as NG,NG dimethylarginine. Ethionine (0.5 mg/g body wt) was found to inhibit in vivo methylation of lysine to form epsilon-N-mono, di and trimethyllysine, 46, 52 and 68%, respectively. The formation of NG,NG-dimethylarginine was inhibited by 85%. Ethylation of these proteins was also studied by giving [ethyl-3H]ethionine. After hydrolysis, the non-histones were found to contain a labeled lysine and arginine derivative, but in the histone fraction only labeled lysine was found. (Author abstract) (21 Refs)

ALTERATION OF MIXED FUNCTION OXIDASES BY CARCINOGENS

93. ROLE OF MIXED-FUNCTION OXIDASES IN THE FORMATION OF BIOLOGICAL REACTIVE INTERMEDIATES.

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Adv Exp Med Biol; 136(partA):23-38 1982

Mixed-function oxidases (MFO) in activation of carcinogens and toxic chemicals, toxicity of oxygen in different species, multiplicity of cytochrome P-450 (CP-450), carcinogenicity of cytochrome P-448 (CP-448), and the role of CP-448 in the formation of reactive intermediates are discussed. CP-450 coupled with superoxide dismutase and catalase has the propensity to convert molecular oxygen into water, thereby removing from the cell the excess of molecular oxygen which might otherwise be converted into singlet oxygen and other reactive and toxic forms of oxygen. CP-450 and MFO in mammalian liver and other tissues are located in the rough and smooth endoplasmic reticulum. The earliest events in malignant cell transformation involve changes in synthesis of glycoproteins by epithelial tissues, resulting in impaired synthesis of mucus, changes in character of the glycocalyx, and changes in lysosomal enzyme structure and function. In studies on the formation of ligand complexes with CP-450 with the reactive carbene intermediate from safrole, the loss of CP-450 activity was observed with emergence of MFO activity characteristic of CP-448. CP-450 and CP-448 show no marked difference in their affinities for substrates but do exhibit major differences in the nature of oxygenated products. Some differences in the catalytic activities of the two cytochromes are presented. Whereas the MFO activity of CP-450 generally leads to the detoxication of environmental chemicals, oxygenation by CP-448 may lead to bay-region oxygenation and to formation of reactive intermediates and proximate carcinogens. CP-448 is characteristic of malignant and neonatal tissue, and is associated with the loss of ribosomes from the endoplasmic reticulum, and with changes in glycoprotein synthesis. (41 Refs)

94. RESPONSE OF THE D-T DIAPHORASE OF LYMPHOID ORGANS OF THE RAT TO POLYCYCLIC HYDROCARBONS CARCINOGENS: A BIOCHEMICAL AND HISTOCHEMICAL STUDY (MEETING ABSTRACT)

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71st Annual Meeting of the International Academy of Pathology (United States-Canadian Division), March 1-5, 1982, Boston, Massachusetts. International Academy of Pathology 95 pp., 1982.

The effects of benzo(a)pyrene, 3-methylcholanthrene, and benzanthracene on the activity of NAD(P)H dehydrogenating enzymes were studied biochemically and histochemically in rat spleen, lymph nodes, and thymus. After the treatment, it was found that the biochemical activity of the soluble D-T diaphorase increased severalfold, whereas the microsomal and mitochondrial NAD(P)H dehydrogenases were unchanged. Histochemically, a marked increase of NAD(P)H-NBT reductase was also observed in the three organs. The histochemical enzymatic activity is mainly localized in areas of T lymphocytes predominance and histiocytes. The lymphocytes in germinal centers were only stained when longer incubation times were used. These results suggest: (1) the D-T diaphorase of lymphoid organs is induced by carcinogens; (2) the increased staining of the NAD(P)H-NBT reductase in treated animals represents the histologic distribution of the D-T diaphorase in spite of the unspecificity of the staining; (3) the staining for the NAD(P)H-NBT reductase may be used as a marker for T lymphocytes under controlled conditions, and, (4) the histochemical staining may represent a real quantitative biochemical difference between B and T lymphocytes. (no Refs)

95. INHIBITORS OF HEPATIC MIXED-FUNCTION OXIDASES. 4. EFFECTS OF BENZIMIDAZOLE AND RELATED COMPOUNDS ON ARYL HYDROCARBON HYDROXYLASE ACTIVITY FROM PHENOBARBITONE AND 3-METHYLCHOLANTHRENE INDUCED RATS.

Little PJ, Ryan AJ
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J Med Chem; 25(6):622-626 1982

A series of 2-n-alkylbenzimidazoles inhibited cytochrome P-450 dependent aryl hydrocarbon hydroxylase (AHH) and aminopyrine N-demethylase (APDM) activities in phenobarbitone (PB) induced rat liver microsomes. 2-Undecylbenzimidazole was the most potent compound in the series, having I50 values of 1.8 x 10(-5) and 1.5 x 10(-5) M against AHH and APDM activities, respectively. Inhibitory activity increased with increasing carbon chain length of the 2-substituent. Regression analysis showed that there was an apparent relationship between inhibitory activity and hydrophobicity (expressed as the octanol/water partition coefficient) for the inhibition of both AHH and APDM activities in PB-induced rat liver microsomes. In contrast, these compounds showed little or no inhibitory activity toward cytochrome P-448 dependent AHH activity in hepatic microsomes from 3-methylcholanthrene (3-MC) treated rats. Two 5,6-dimethylbenzimidazoles showed slight inhibitory activity and naphtho[2,3:4',5']imidazole was only threefold less active toward 3-MC-induced (I50 = 2.6 x 10(-4) M) than PB-induced (I50 = 8.4 x 10(-5)) AHH activity. These results suggest that for nitrogen heterocycles there may be a relationship of increasing polycyclic size and increasing inhibitory activity toward AHH activity in 3-MC-induced rat liver microsomes. (Author abstract) (32 Refs)

96. EFFECTS OF ALPHA-NAPHTHYLISOTHIOCYANATE, LITHOCHOLIC ACID AND SELECTED HEPATOCARCINOGENS ON EPOXIDE HYDROLASE, DT-DIAPHORASE AND SERUM INDICATORS OF CHOLESTASIS (MEETING ABSTRACT)

Thompson MB, Dent JG, Graichen ME, Neptun DA, Scortichini BH, Popp JA
Chemical Industry Institute of Toxicology, Research Triangle Park, NC, 27709
Toxicologist; 2(1):101 1982

The classic cholestatic agent alpha-naphthylisothiocyanate (ANIT) elevates the hepatic preneoplastic marker epoxide hydrolase (EH). Abilities of 3 hepatocarcinogens and 2 cholestatic agents to produce cholestasis and enhance hepatic EH activity were compared. Hepatocarcinogens 2-acetylaminofluorene (AAF) at 100 ppm or 3'-methyl-4-dimethylaminoazobenzene (3'-MeDAB) at 600 ppm in the diets or diethylnitrosamine (DEN) at 40 ppm in the drinking water were given to male, Fischer-344 rats (200-270 g). The cholestatic agents ANIT at 1000 ppm or lithocholic acid (LA) at 10,000 ppm in the diets were fed to comparable groups. Concentrations of total bile acids (BA), total cholesterol (CH) and total bilirubin (BIL) and the activity of gamma-glutamyltranspeptidase (GGT) were measured in serum at 2, 4 and 6 weeks. Activities of hepatic microsomal epoxide hydrolase (EH) and cytosolic DT-diaphorase (DTD) were determined. Serum BA concentrations were increased by all treatments. ANIT treatments produced the greatest increases. AAF an 3'-MeDAB caused intermediate increases and DEN and LA the smallest. CH and BIL concentrations and activities of GGT and DTD were only increased by treatment with ANIT. EH was increased by all treatments except LA. At 2 and 6 weeks animals exposed to AAF, DEN and 3'-MeDAB had a direct correlation between serum BA and EH activities. (no Refs)

97. REACTIVE METABOLITES AS KEY INTERMEDIATES IN PHARMACOLOGIC AND TOXICOLOGIC RESPONSES: EXAMPLES FROM CHEMICAL CARCINOGENESIS.

Miller EC, Miller JA
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Adv Exp Med Biol; 136(partA):1-21 1982

Electrophilic reactants as toxic agents, mechanism of chemical carcinogenesis, and metabolic activation of chemical carcinogens (CC) and of 1'-hydroxyestragole (HE) are discussed. Current data on carcinogenesis indicate that the first stage, initiation, depends on the reaction of a strong electrophilic reactant (ER) with DNA and a resultant mutation of the DNA. The second stage, promotion, requires a prolonged time for completion and appears to be reversible in the early phases. The activation reactions of critical importance in the induction of tumors are influenced by the many factors (molecular geometry, polarity) that determine the approach of the procarcinogen or proximate carcinogen to the enzyme(s), the properties of the enzyme(s) in relation to the particular substrate, and the susceptibility of ER to inactivating reactions before they reach the critical target for the induction of neoplasia. Examples of some reactions for the activation of procarcinogens to ER are summarized and the metabolic activation of a broader range of CC is shown. The characterization of the DNA adducts formed from HE was studied in mouse liver. Co-chromatography in three system showed the apparent identity of the principal products formed in vivo with the principal products formed by reaction of 1'-acetoxyestragole with deoxyguanosine (3 products) and deoxyadenosine (1 product). Data suggested that each of the deoxyguanosine adducts was substituted on the exocyclic amino group. The mutagenic and carcinogenic responses of cells to the attack by chemicals depend on the genes in the DNA that are affected, the susceptibility of the modified nucleic acid residues to repair, the fidelity of the repair, and the effects of unrepaired lesions on DNA replication. (56 Refs)

98. METABOLIC ACTIVATION AND HEPATOTOXICITY OF TRICHLOROETHYLENE.

Reynolds ES, Moslen MT
Chemical Pathology Lab., Dept. Pathology, Univ. Texas Medical Branch, Galveston, TX
Adv Exp Med Biol; 136(partA):693-701 1982

Recent studies are reviewed which attempted to elucidate the relationship between the metabolism and hepatotoxicity of trichloroethylene (TCE). These studies involved pretreatment of animals with phenobarbital and other inducers of cytochrome P-450 (Aroclor 1254, 3-methylcholanthrene, hexachlorobenzene, and pregnenolone-1 alpha-carbonitrile). A significant correlation was noted between the magnitude of liver injury in a pretreatment group and level of hepatic cytochrome P-450. Effects of liver injury produced by TCE anesthesia are described. An oral dosing system is now being used where the dose of TCE can be more readily controlled. The present working hypothesis remains that TCE is oxidized by a cytochrome P-450 dependent process to reactive electrophilic species which attack and denature structural and functional components of the cell, which could account for the rapid deactivation of cytochrome P-450 and early increases in the permeability of the plasma membrane to Na^+ and Ca^{++}. While the identity of these reactive species of TCE remains unknown, some speculation on their identity is discussed. (12 Refs)

99. EFFECTS OF CHLORINATED PARAFFINS ON SOME DRUG-METABOLIZING ENZYMES IN RAT LIVER AND IN THE AMES TEST.

Meijer J, Rundgren M, Astrom A, DePierre JW, Sundvall A, Rannug U
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Adv Exp Med Biol; 136(partA):821-828 1982

Influence of chlorinated paraffins (CP) on induction of drug-metabolizing enzymes in rat liver and mutagenic effect in the Ames test are discussed. Results of induction of drug-metabolizing enzymes in rat liver by CP are presented. The liver-somatic index increased and the amount of cytochrome P-450 was not changed. The activity of microsomal epoxide hydrolase was not affected by treatment with Cereclor 42, but the activity increased 30, 90, and 200-330% after treatment with Cereclor S58, 70, and 70L, respectively. SDS-polyacrylamide gel electrophoresis was performed to compare the proteins of liver microsomes from control and induced rats. The same polypeptide pattern was observed in both groups of animals and some of the bands were increased in the treated rats. No toxic effects were noted in any of the strains in the Ames test and no differences in the number of revertants with the strains TA 1537 and TA 100 were observed. Strain TA 98 showed a slight increase in the number of revertants in the presence of S-9 fraction. This low increase may have arisen by chance since no dose related effects were observed with Cereclor 70L. Furthermore the lack of toxic effects may indicate that paraffin does not penetrate into bacterial cells. Possible modes of metabolism of Cereclor 70L include dechlorination and oxidation of the carbon chain. Metabolism of CP may also be related to their ability to induce epoxide hydrolase and glutathione S-transferase. (16 Refs)

ALTERATION OF OTHER CARCINOGEN-METABOLIZING ENZYMES BY CARCINOGENS

100. EFFECT OF 3-METHYLCHOLANTHRENE ON RNA POLYMERASE AND PROTEIN KINASE ACTIVITIES OF TRANSCRIPTIONALLY ACTIVE CHROMATIN SUBFRACTION IN RAT LIVER.

Szeberenyi J, Kleeberg U, Tigyi A
Dept. Biology, Univ. Medical Sch., Pecs, Hungary
Experientia; 38(6):687-689 1982

The activities of RNA polymerases and nuclear protein kinases were determined in subfractions of rat liver nuclei after a single dose of the polycyclic aromatic hydrocarbon 3-methylcholanthrene (3-MC). Both enzyme activities as well as the in vivo phosphorylation of chromatin proteins were enhanced by 3-MC in the transcriptionally active subfraction of chromatin. (Author abstract) (18 Refs)

101. EXPERIMENTAL STUDY OF FUNCTIONAL STATE AND ENZYMATIC STRUCTURE OF PULMONARY ALVEOLAR MACROPHAGES AFTER PERORAL EXPOSURE TO DIMETHYLNITROSAMINE.

Merkur'eva RV, Litvinov NN, Aulika BV, Mukhambetova LKh, Bushinskaia LI, Dolinskaia SI, Iakimova ER, Konstantinova IN, Votiakov AV
Lab. Biochemistry, A. N. Sysin Inst. General and Community Public Health, Moscow, USSR
Biull Eksp Biol Med; 93(4):41-43 1982

Effect of peroral exposure to dimethylnitrosamine (DMNA: 30 mg/kg) on pulmonary alveolar macrophages was studied in male random-bred albino rats. DMNA administration produced progressive decrease of the number of viable alveolar macrophages. The decrease of macrophage count was associated with the increase of activities of microsomal acetylesterase and lysosomal beta-glucuronidase and the decrease of activity of mitochondrial malate dehydrogenase. (8 Refs) (In RUS)

102. HISTOCHEMICAL ELUCIDATION OF HAMSTER PANCREATIC CARCINOGENESIS INDUCED BY N-NITROSO-BIS(2-HYDROXYPROPYL) AMINE.

Miyazaki K, Takasan H, Hamashima Y
1st Dept. Surgery, Faculty Medicine, Kyoto Univ., Sakyo-ku, Kyoto 606, Japan
Nippon Geka Hokan; 51(1):3-13 1982

Hamster pancreatic carcinogenesis induced by 500 mg/kg/wk sc N-nitroso-bis(hydroxypropyl) amine (DHPN) was studied in 20 outbred 8-wk-old Syrian golden hamsters. Pathological and histological changes were observed 4-27 wk after the induction of carcinogenesis. The most frequent change observed was multilayer hyperplasia of intralobular ductules. After 22 wk adenocarcinomas were observed. The distribution and intensity of enzyme activity is listed. In adenocarcinomas, strong activities of alkaline phosphatase, succinate dehydrogenase, lactate dehydrogenase (LDH), glucose-6-phosphatase (G-6-PD), and NADH-tetrazolium reductase were observed. Moderate activity of LDH and G-6-PD was proved in the epithelium of adenocarcinomas. In the control group, ^3H-thymidine uptake (TU) was observed in all tissues components. TU of the acinar cells, interlobular ductules (ILD), and main pancreatic ducts was greater than that of islet cells. After DHPN administration, a significant increase of TU was observed. No TU increase was observed in islet cells. TU of flat epithelial and hypertrophic multiplications and multilayer hyperplasia of ILD was greater than in controls. TU of hypertrophic epithelial multiplications was significantly greater than that of flat. TU of adenocarcinoma epithelium was significantly greater than that of other lesion and normal tissue components. The differences of serum ribonuclease and amylase activity between DHPN-treated and control animals are presented. (17 Refs)

103. SEQUENTIAL 2-ACETYLAMINOFLUORENE-PHENOBARBITAL EXPOSURE INDUCES A CYTOSOLIC ALDEHYDE DEHYDROGENASE DURING RAT HEPATOCARCINOGENESIS.

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Carcinogenesis; 3(5):533-538 1982

A significant change in hepatic aldehyde dehydrogenase activity has been observed in normal Sprague-Dawley rat liver during the promotion phase of hepatocarcinogenesis induced by brief feeding of 2-acetylaminofluorene (2-AAF) followed by tumor promotion using dietary phenobarbital (PB) exposure. Animals receiving only 2-AAF or PB do not possess this new aldehyde dehydrogenase activity. The phenotype is characterized by the appearance of a new cytosolic isozyme kinetically, electrophoretically and immunochemically distinct from the normal liver aldehyde dehydrogenase isozymes and from aldehyde dehydrogenases inducible in 2-AAF-induced hepatomas. The new isozyme is NAD-dependent, disulfiram-sensitive and cross-reacts with antiserum to a normal liver aldehyde dehydrogenase inducible in several lines of rats by PB. However, the population of animals used in this study has been shown previously to be non-responsive to aldehyde dehydrogenase induction by dietary PB. Since no animals receiving only PB express this new isozyme, the carcinogen must play a significant role in its induction. Moreover, that not all animals receiving carcinogen and promoter possess the phenotype suggests this carcinogen/promoter interaction has a genetic basis. (Author abstract) (19 Refs)

104. REACTION OF MICROSOMAL AND CYTOSOLIC ENZYMES WITH N-ARYLACETOHYDROXAMIC ACIDS IN THE PRESENCE OF OXYGEN.

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Adv Exp Med Biol; 136(partB):951-970 1982

Experiments on the metabolic fate of N-hydroxy-4-chloroacetanilide (N-OH-4ClAA), N-hydroxy-2-acetylaminofluorene (N-OH-2AAF), N-hydroxy-4-acetylaminobiphenyl (N-OH-4AAB), and N-hydroxyphenacetin (NHP) in rabbit or rat liver microsomal and cytosolic systems are reviewed. Differences in substrate affinity cause microsomal and cytosolic N-OH-2AAF, N-OH-4AAB, N-OH-4ClAA, and NHP to be N-deacylated at different rates, but the differences are not clear-cut enough to permit differentiation between carcinogenic polycyclic and noncarcinogenic monocyclic compounds. Differences in the rates of oxidation of the corresponding arylhydroxyamines were also detected, but these were likewise not clear enough for separation of respective poly- and monocyclic compounds. Clear differences in reactivity between poly- and monocyclic nitrosoarenes were observed, but have not been related to toxicity of the corresponding N-arylacetohydroxamic acids. The prominent reactivity of N-OH-2AAF and of 2-nitrosofluorene suggests that the primary lesion, from which tumor growth is initiated, may be caused by this arylhydroxylamine and/or its N-arylacetohydroxamic acid. (38 Refs)

105. EFFECTS OF LINDANE TREATMENT ON DRUG METABOLIZING ENZYMES AND LIVER WEIGHT OF CF1 MICE IN WHICH IT EVOKED HEPATOMAS AND IN NON-SUSCEPTIBLE RODENTS.

Oesch F, Friedberg T, Herbst M, Paul W, Wilhelm N, Bentley P
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Chem Biol Interact; 40(1):1-14 1982

The specific activities of some enzymes which are thought to be involved in the metabolism of lindane were studied in three different mouse strains in order to investigate whether differences exist in the activities of these enzymes. Because the enzyme pattern may change after lindane treatment during the carcinogenicity studies, we also investigated the enzyme activities in animals treated for 3 days or 3 mo with various doses of lindane. The influence of lindane treatment on the relative liver wt was also determined. Basal glutathione-S-transferase activity was higher in males than in females in all three strains, bearing no apparent relationship to susceptibility for tumor formation. However, after treatment with the highest dose of lindane a five- to six-fold induction of this enzyme activity was observed in female CF1 mice, which then together with the male CF1 mice had a higher glutathione-S-transferase activity than untreated and treated B6C3F1 mice and Osborne-Mendel rats. Whether lindane or one of its metabolites is activated by conjugation with glutathione remains to be established. After treatment of the animals with high doses of lindane detergent-treated rat liver microsomes showed a higher UDP-glucuronosyltransferase activity than mouse liver microsomes. This high activity could lead to a rapid conjugation of phenols derived from lindane. The most striking difference observed in this study was the fact that together with the larger increase in absolute and relative liver wt, untreated and treated CF1 mice showed higher monooxygenase activity and, after treatment with lindane, lower epoxide hydrolase activity than rats. Whether the monooxygenase and epoxide hydrolase activities will lead to an accumulation of reactive epoxides derived from lindane remains to be clarified. (18 Refs)

REVIEWS AND OTHER RELEVANT STUDIES

106. METABOLISM OF CHEMICAL CARCINOGENS.

Weisburger JH, Williams G
American Health Foundation, Naylor Dana Inst. for Disease Prevention, Valhalla, NY
Cancer - A Comprehensive Treatise Vol. 1. Etiology - Chemical and Physical Carcinogenesis. Second Edition. Becker FF, ed. New York, Plenum Press, 714 pp., 1982.

Chemical carcinogens are defined by their ability to induce tumors. Four types of response have generally been accepted as evidence of tumorigenicity. These include an increased incidence of the tumor types occurring in controls, the occurrence of tumors earlier than in controls, the development of types of tumors not seen in controls, and an increased multiplicity of tumors in individual animals. Examples of the genotoxic carcinogen class include alkylating agents which are activation independent, aromatic amines and polycyclic aromatic hydrocarbons which are activation-dependent, and metals. Examples of the epigenetic carcinogen class include plastics and asbestos, estrogen, androgen, purine analog, and phorbol ester. Promotors are agents that increase the tumorigenic response to a carcinogen when applied after the carcinogen. Genetic factors, sex and endocrine status, age, diet, activities of intestinal flora, the presence of other chemicals, the mode and frequency of exposure, and numerous other factors influence the variation in carcinogen metabolism. Research during the last few decades has pinpointed natural products as major causes of cancer in humans in various parts of the world. (486 Refs)

107. CANCER: A COMPREHENSIVE TREATISE. VOLUME 1. ETIOLOGY: CHEMICAL AND PHYSICAL CARCINOGENESIS. SECOND EDITION.

Becker FF
Univ. Texas System Cancer Center, M.D. Anderson Hosp. and Tumor Inst., Houston, TX
Cancer: A Comprehensive Treatise. Volume 1. Etiology: Chemical and Physical Carcinogenesis. Second Edition. New York, Plenum Press, 714 pp., 1982.

In order to eradicate cancer, carcinogenic agents must be identified and their mechanism of action, understood. Crucial interactions between these carcinogens and important macromolecules within the cell must be identified, and those which relate to carcinogenesis must be distinguished from those which are extraneous. The alterations of cell function induced by these reactions must be examined so that phenotypic variation may be understood and an explantation provided for why malignant cells escape from normal homeostatic control. Malignancy must be defined so that the characteristics of cellular activity that permit the malignant cell to compete so effectively with the normal constituent can be defined. The goals of cancer research in general and of the present text are reflected in chapters on cytogenetics, hormones, immunocompetence, chemical carcinogenesis, metabolism of chemical carcinogens, interactions of carcinogens with nucleic acids, effects of carcinogens on cell organelles, sequential aspects and effects in chemical carcinogenesis, radiation, radiation carcinogenesis, and cancer associated with asbestosis, schistosomiasis, foreign bodies, and scars. (3320 Refs)

108. SEQUENTIAL ASPECTS OF CHEMICAL CARCINOGENESIS: SKIN.

Berenblum I
Weizmann Inst. Science, Rehovot, Israel
Cancer - A Comprehensive Treatise Vol. 1. Etiology - Chemical and Physical Carcinogenesis. Second Edition. Becker FF, ed. New York, Plenum Press, 714 pp., 1982.

The two-stage hypothesis, the initiation-promotion hypothesis, was based on animal studies of sequential stages of skin carcinogenesis. Initiators for skin carcinogenesis include 2-acetylaminofluorene, UV light, beta-radiation, certain metabolites of 'complete' carcinogens, various alkylating agents and mutagens. Promoters for skin carcinogenesis include physical agents, 'complete' chemical carcinogens, non- or weakly-acting skin carcinogens, croton oil, straight-chain N-alkanes, phenolic compounds, extracts of tobacco leaf, and extracts of tobacco smoke condensates. The two-stage system in skin carcinogenesis has been extended, based on further experiments. Evidence that a mutational change in the DNA genome was responsible for the initiating change of carcinogenesis is based on the ability of most carcinogens to bind with DNA and that there is a fairly good correlation between mutagenic and carcinogenic properties among a wide range of compounds. Evidence for the stimulation of synthetic processes in the cell includes the stimulation of DNA and RNA synthesis as well as protein and phospholipid synthesis. The effects of enzymatic functions in the cell are based on an increase in proteinase activity, on stimulation of ornithine decarboxylase activity, on changes in cyclic nucleotide levels, and on a decrease in histidase activity. (378 Refs)

109. CYTOLOGIC AND BIOCHEMICAL GENETIC EFFECTS OF CHEMICAL CARCINOGENS. ANNUAL REPORT, 1 JUL. 1980-30 JUN. 1981.

Rasmussen RE
Ohio Aerospace Medical Res. Lab., Wright-Patterson Air Force Base, OH
Sci Tech Aerosp Rep; 20(8):1128 1982

The first project is concerned with the relationship between initiation of cancer by chemicals and the damage and repair of DNA in cells and tissues susceptible to the carcinogenic action of the chemicals. The working hypothesis is that interaction of the carcinogen with cellular DNA is a necessary step in carcinogenesis and that this interaction may cause DNA damage which is then followed by DNA repair synthesis. The second project was conducted with the cooperation of the staff of the Toxic Hazards Research Unit at AMRL, WPAFB. Rats and hamsters were exposed by inhalation to hydrazine at 750 ppm for 1 hr. Groups of animals which had been exposed only once or which had been exposed 10x were shipped to UC Irvine for study. The factors studied were (1) DNA replication in the lung; (2) DNA repair synthesis in the lung; (3) Cellular replication in the lung and nasal turbinates; and (4) Metabolism of a known lung carcinogen, 3H-benzo(a)pyrene, by lung slices from the treated animals. The third project was initiated during the current year with the goal of developing an animal model in which biochemical and cytogenetic factors could be studied during the process of tumorigenesis. Range-finding studies are underway at the Toxic Hazards Research Unit (THRU) to establish the intratracheal dosage of 3-methylcholanthrene (MCA) necessary to produce a high yield of lung tumors in Fischer 344 rats within 12 mo. (Author abstract)

110. CARCINOGEN-MEDIATED AMPLIFICATION OF SPECIFIC DNA SEQUENCES.

Lavi S
Dept. Virology, Weizmann Inst. Science, Rehovot, Israel
J Cell Biochem; 18(2):149-156 1982

The development of a experimental system model , which utilizes simian virus 40 (SV40)-transformed Chinese hamster embryo cells, coupled with a highly sensitive in situ hybridization procedure for the detection of a single cell in which viral DNA synthesis has been induced, is presented. When exposed to chemical carcinogens such as benzo(a)pyrene, N-methyl-N'-nitro-N-nitrosoguanidine, 7,12-dimethyl benz(a)anthracene (DMBA), ethyl methanesulfonate aflatoxin B1, and 3-methylcholanthrene or physical carcinogens (gamma or UV radiation), SV40 DNA synthesis was induced in treated cells. Noncarcinogenic compounds such as phenanthrene and dibenz(a,c)anthracene had no effect. While carcinogen-induced amplification of SV40 DNA sequences is controlled by the viral 'A' gene, no infectious virus or complete SV40 DNA molecules were found in treated cells. DMBA treatment induced a heterogenous collection of DNA molecules with SV40 sequences. Analysis of Hirt's supernatant using restriction enzyme analysis of the amplified DNA molecules indicated that not all sequences in the integrated SV40 inserts are present. Amplification of SV40 DNA sequences may reflect a more general gene amplification phenomenon mediated by chemical carcinogens. (19 Refs)

111. TOXICITY OF POLYBROMINATED BIPHENYLS (PBBS) IN DOMESTIC AND LABORATORY ANIMALS.

Damstra T, Jurgelski W, Posner HS, Vouk VB, Bernheim NJ, Guthrie J, Luster M, Falk HL
Natl. Inst. Environmental Health Sciences, Post Office Box 12233, Research Triangle Park, NC, 22709
Environ Health Perspect; 44():175-188 1982

Chemical composition and fate of polybrominated biphenyls (PBBs) in the environment, absorption, distribution, biotransformation, and elimination of PBBs, enzyme induction by PBBs, chemical interaction of PBBs with other chemicals and drugs, general toxicity, neurobehavioral toxicity, immunotoxicity, reproductive toxicity, mutagenicity, and carcinogenicity of PBBs involved in accidental contamination of cattle feed in Michigan in 1973 are reviewed. Mutagenicity studies on PBBs to date have been negative but inadequate. Exposure to high doses of PBBs have been shown to cause liver cancer in rats and mice. (117 Refs)

112. HEREDITARY ADENOMATOSIS OF THE COLON AND RECTUM: RELEVANCE TO CANCER PROMOTION AND CANCER CONTROL IN HUMANS.

Kopelovich L
Memorial Sloan-Kettering Cancer Center, 1275 York Ave., New York, NY, 10021
Cancer Genet Cytogenet; 5(4):333-351 1982

Means of detecting persons at risk for colorectal cancers are described. SF cells, derived from normal-appearing biopsies of ACR gene carriers, appear to exist in an initiated state as the result of a dominant mutation. Topics discussed in relation to ACR and SF cells and colorectal neoplasms include the following: membrane-associated parameters, metabolic alterations, differential susceptiblity to transformation by chemical and physical agents and oncogenic viruses, cancer-related antigens, tissue culture studies, tumor promotion, genetic mechanisms, and cancer prognosis and control. (141 Refs)

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NOTICE OF CURRENT REVIEWS: CARCINOGENESIS

As an additional service to readers of carcinogenesis (CK series) CANCERGRAMS, each issue now provides a bibliography of review articles of interest to carcinogenesis researchers, selected from journals screened for that month's CANCERGRAMS.

CHEMICAL CARCINOGENESIS

1. TOXICITY OF POLYBROMINATED BIPHENYLS (PBBS) IN DOMESTIC AND LABORATORY ANIMALS.

Damstra T, Jurgelski W, Posner HS, Vouk VB, Bernheim NJ, Guthrie J, Luster M, Falk HL

Natl. Inst. Environmental Health Sciences, Post Office Box 12233, Research Triangle Park, NC, 22709

Environ Health Perspect; 44(1):175-188 1982

2. CHLOROFORM: A REVIEW OF ITS METABOLISM, TERATOGENIC, MUTAGENIC, AND CARCINOGENIC POTENTIAL.

Davidson IW, Sumner DD, Parker JC

(c/o Parker) ECAO, Environmental Protection Agency, MD-52, Research Triangle Park, NC, 27711

Drug Chem Toxicol; 5(1):1-87 1982

3. FORMALDEHYDE IN PRESENT-DAY ENVIRONMENTAL TOXICOLOGY.

Beritic T, Kovac S, Dimov D

Odjel za profesionalne bolesti, Institut za medicinska istrazivanja i medicinu rada, Zagreb, Yugoslavia

Arh Hig Rada Toksikol; 32(4):363-395 1981

In SCR

4. HORMONES AS ETIOLOGICAL AGENTS IN NEOPLASIA.

Furth J

Inst. Cancer Res., Columbia Univ. Coll. Physicians and Surgeons, New York, NY

Cancer - A Comprehensive Treatise Vol. 1. Etiology - Chemical and Physical Carcinogenesis. Second Edition. Becker FF, ed. New York, Plenum Press, 714 pp., 1982.

5. CURRENT VIEWS ON HORMONES AND BREAST CANCER.

Molinatti GM, Limone P

Cattedra di Endocrinologia, Universita di Torino, C.so Polonia, 14, 10126 Turin, Italy

Minerva Med; 73(17):1047-1053 1982

In ITA

6. THE CHROMOSOMAL EFFECTS OF THE ORAL CONTRACEPTIVE.

Bishun NP

Tissue Culture and Cytogenetics Unit, Res. Dept., Marie Curie Memorial Foundation, The Chart, Oxted, Surrey, England

J Surg Oncol; 20(2):115-118 1982

7. TOXICITY AND CARCINOGENICITY OF NICKEL AND ITS COMPOUNDS. A REVIEW OF THE CURRENT STATUS.

Raithel HJ, Schaller KH

Institut fur Arbeits- und Sozialmedizin, Poliklinik fur Berufskrankheiten, Universitat Erlangen-Nurnberg, Schillerstrasse 25-29, D-8520 Erlangen, W. Germany

Zentralbl Bakteriol Mikrobiol Hyg [B]; 173(1/2):63-91 1981

In GER

8. HISTORICAL OVERVIEW OF NITROSOUREA DEVELOPMENT.

Goldin A

Div. Cancer Treatment, NCI NIH, Building 37, Room 5E20, Bethesda, MD, 20205

INSERM Symp; 19:3-11 1981

9. PATHOLOGY.

Goyer RA

Natl. Inst. Environmental Health Sciences, Research Triangle Park, NC

JAMA; 247(21):2973-2975 1982

RADIATION CARCINOGENESIS

10. IDENTIFYING THE HEALTH RISKS FROM VERY LOW-DOSE SPARSELY IONIZING RADIATION.

Dreyer NA, Friedlander E

Epidemiology Resources, Inc., P.O. Box 57, Chestnut Hill, MA, 02167

Am J Public Health; 72(6):585-588 1982

11. RISK OF RADIOLOGICAL EXAMINATIONS.

Jankowski

Instytut Medycyny Pracy w Lodzi, ul. Olowiana 6, 91-614 Lodz, Poland

Pol Przegl Radiol; 45(6):383-386 1981

In POL

12. RADIOBIOLOGY OF RISK ESTIMATES IN MEDICAL IRRADIATION (MEETING ABSTRACT)

Rossi HH

Columbia University, New York, NY

IN: 148th National Meeting of the American Association for the Advancement of Science, January 3-8, 1982, Washington, D.C American Association for the Advancement of Science 182 pp., 1982.

13. RADIATION-INDUCED VASCULAR INJURY AND ITS RELATION TO LATE EFFECTS IN NORMAL TISSUES.

Law MP

MRC Cyclotron Unit, Hammersmith Hosp., London W12 OHS, England

Adv Radiat Biol; 9:37-73 1981

14. CURRENT CONCEPTS IN ULTRAVIOLET CARCINOGENESIS.

Granstein RD, Sober AJ

(c/o Sober) Dept. Dermatology, Massachusetts General Hosp., Boston, MA, 02114

Proc Soc Exp Biol Med; 170(2):115-125 1982

15. METABOLIC CHANGES AFTER EXPOSURE TO RADIONUCLIDES.

Kalistratova VS

No affiliation given

Med Radiol (Mosk); 27(4):62-71 1982

In RUS

DIETARY FACTORS IN CARCINOGENESIS

16. CAFFEINE: AN UPDATE.

Oser BL, Ford RA

Bernard L. Oser and Associates, 108-18 Queens Blvd., Forest Hills, NY, 11375

Drug Chem Toxicol; 4(4):311-329 1981

17. ANALYSIS OF MUTAGENIC EFFECTS OF FOREIGN SUBSTANCES IN THE FOOD PRODUCTS.

Maganova NB

Inst. Nutrition, Moscow, USSR

Vopr Pitan; (2):3-8 1982

In RUS

EPIDEMIOLOGY, ETIOLOGY AND GENETIC ASPECTS OF HUMAN CANCER

18. RADIATION EPIDEMIOLOGY (MEETING ABSTRACT)

Marks S

No affiliation given

148th National Meeting of the American Association for the Advancement of Science, January 3-8, 1982, Washington, D.C. American Association for the Advancement of Science 182 pp., 1982.

19. EPIDEMIOLOGICAL STUDIES ON RADIATION CARCINOGENESIS IN HUMAN POPULATIONS FOLLOWING ACUTE EXPOSURE: NUCLEAR EXPLOSIONS AND MEDICAL RADIATION.

Fabrikant JI

Donner Lab., Univ. California, Berkeley, CA, 94720

Yale J Biol Med; 54(6):457-469 1981

20. EPIDEMIOLOGIC APPROACH TO CANCER.

Guinee VF

Dept. Epidemiology, Univ. Texas System Cancer Center, M.D. Anderson Hosp. and Tumor Inst., Houston, TX

Cancer - A Comprehensive Treatise Vol. 1. Etiology - Chemical and Physical Carcinogenesis. Second Edition. Becker FF, ed. New York, Plenum Press, 714 pp., 1982.

21. EPIDEMIOLOGY AND EARLY DETECTION OF CANCER OF THE ESOPHAGUS.

Sorouri P

900 Hillside Road, Wilmington, DE, 19807

Gastrointestinal Cancer 1. Decosse JJand Sherlock P, ed. The Hague, Martinus Nijhoff Publishers, Cancer Treatment and Research, Vol. 3, 452 pp., 1981.

22. METABOLIC EPIDEMIOLOGY OF LARGE BOWEL CANCER.

Hill MJ

Central Public Health Lab., Colindale Ave., London NW9, England

Gastrointestinal Cancer 1. Decosse JJand Sherlock P, ed. The Hague, Martinus Nijhoff Publishers, Cancer Treatment and Research, Vol. 3, 452 pp., 1981.

23. EPIDEMIOLOGY OF GASTRIC CANCER AND ITS PRECURSOR LESIONS.

Correa P

Louisiana State Univ. Medical Center, New Orleans, LA, 70112

Gastrointestinal Cancer 1. Decosse JJand Sherlock P, ed. The Hague, Martinus Nijhoff Publishers, Cancer Treatment and Research, Vol. 3, 452 pp., 1981.

24. TRENDS IN THE INCIDENCE OF GASTRIC CARCINOMA (MEETING ABSTRACT)

Nobrega FT

Preventive and Internal Medicine, Mayo Clinic, Rochester, MN

Eleventh Annual William Beaumont Gastrointestinal Symposium, March 24-26, 1982, El Paso, Texas. William Beaumont Army Medical Center 56 pp., 1982.

25. CANCER IN INFLAMMATORY BOWEL DISEASE.

Bayless TM, Yardley JH

Johns Hopkins Hosp., Baltimore, MD, 21205

Gastrointestinal Cancer 1. Decosse JJand Sherlock P, ed. The Hague, Martinus Nijhoff Publishers, Cancer Treatment and Research, Vol. 3, 452 pp., 1981.

26. GENETIC ASPECTS OF GUT CANCER.

McConnell RB

Broadgreen Hosp., Liverpool, England

Gastrointestinal Cancer 1. Decosse JJand Sherlock P, ed. The Hague, Martinus Nijhoff Publishers, Cancer Treatment and Research, Vol. 3, 452 pp., 1981.

27. HOST AND ENVIRONMENTAL FACTORS ENHANCING CARCINOGENESIS IN THE RESPIRATORY TRACT.

Nettesheim P, Topping DC, Jamasbi R

Natl. Inst. Environmental Health Sciences, Research Triangle Park, NC, 27709

Annu Rev Pharmacol Toxicol; 21:133-163 1981

ENVIRONMENTAL AND OCCUPATIONAL FACTORS IN CARCINOGENESIS

28. A SEARCH FOR SAFE DRINKING WATER.

Hairsine MA, Schumm HA

Northern Indiana Health Systems Agency, Inc., South Bend, IN

A Search for Safe Drinking Water. Available from National Technical Information Service, Springfield, VA, as HRP-0903845/6, 68 pp., 1981.

29. OCCUPATIONAL EXPOSURES TO URANIUM: PROCESSES, HAZARDS, AND REGULATIONS.

Stoetzel GA, Fisher DR, McCormack WD, Hoenes GR, Marks S

Battelle Pacific Northwest Lab., Richland, WA

Occupational Exposures to Uranium: Processes, Hazards, and Regulations. Available from National Technical Information Service, Springfield, VA, as PNL-3341-USUR-01, 91 pp., 1981.

CELLULAR AND MOLECULAR MECHANISMS IN CARCINOGENESIS

30. THE ROLE OF RADIATION AND CHEMICALS IN THE INDUCTION OF MUTATIONS AND EPIGENETIC CHANGES DURING CARCINOGENESIS.

Trosko JE, Chang CC

Dept. Human Development, Coll. Human Medicine, Michigan State Univ., East Lansing, MI, 48824

Adv Radiat Biol; 9:2-36 1981

31. SOME EFFECTS OF CARCINOGENS ON CELL ORGANELLES

Svoboda DJ, Reddy J

Dept. Pathology and Oncology, Univ. Kansas Coll. Health Sciences, Kansas City, KS

Cancer - A Comprehensive Treatise Vol. 1. Etiology - Chemical and Physical Carcinogenesis. Second Edition. Becker FF, ed. New York, Plenum Press, 714 pp., 1982.

32. CHEMICAL CARCINOGENESIS: INTERACTIONS OF CARCINOGENS WITH NUCLEIC ACIDS

Rajalakshmi S, Prema M, Sarma D

Dept. Pathology, Univ. Toronto, Toronto, Ontario, Canada

Cancer - A Comprehensive Treatise Vol. 1. Etiology - Chemical and Physical Carcinogenesis. Second Edition. Becker FF, ed. New York, Plenum Press, 714 pp., 1982.

33. A MOLECULAR RATIONALE FOR NITROSOUREA INDUCED CYTOTOXICITY.

Tew KD

Lombardi Cancer Center, Div. Medical Oncology, Georgetown Univ., 3800 Reservoir Road, N.W., Washington, DC, 20007

INSERM Symp; 19:61-77 1981

34. MODIFICATION OF DNA AND RNA BASES BY THE NITROSOUREAS

Ludlum DB, Tong WP

Div. Oncology, Dept. Pharmacology and Experimental Therapy, Albany Medical Coll., Albany, NY, 12208

INSERM Symp; 19:21-31 1981

35. CALMODULIN AND CA2+ IN NORMAL AND TRANSFORMED CELLS.

Veigl ML, Sedwick WD, Vanaman TC

Dept. Microbiology and Immunology, Duke Univ. Medical Center, Durham, NC, 27710

Fed Proc; 41(7):2283-2288 1982

36. METABOLISM AND TOXICITY OF AFLATOXINS.

Hsieh DP, Wong JJ

Dept. Environmental Toxicology, Univ. California, Davis, Davis, CA, 95616

Adv Exp Med Biol; 136(partB):847-863 1982

37. REACTION OF MICROSOMAL AND CYTOSOLIC ENZYMES WITH N-ARYLACETOHYDROXAMIC ACIDS IN THE PRESENCE OF OXYGEN.

Lenk W, [illegible] U

Pharmakologisches Institut, Universitat Munchen, Nussbaumstrasse 26, D-8000 Munchen 2, W. Germany

Adv Exp Med Biol; 136(partB):951-970 1982

38. METABOLIC ACTIVATION AND DEACTIVATION MECHANISMS OF DI-, TRI-, AND TETRACHLOROETHYLENES.

Henschler D, Hoos R

Inst. Toxicology, Univ. Wurzburg, Versbacher Strasse 9, Wurzburg D-8700, W. Germany

Adv Exp Med Biol; 136(partA):659-666 1982

39. METABOLIC ACTIVATION AND HEPATOTOXICITY OF TRICHLOROETHYLENE.

Reynolds ES, Moslen MT

Chemical Pathology Lab., Dept. Pathology, Univ. Texas Medical Branch, Galveston, TX

Adv Exp Med Biol; 136(partA):693-701 1982

40. THE ACTIVATING ROLE OF GLUTATHIONE IN THE MUTAGENICITY OF 1,2-DIBROMOETHANE.

van Bladeren PJ, Breimer DD, Rotteveel-Smijs GM, Hoogeterp JJ, Mohn GR, De Groot A, Van Zeeland AA, Van der Gen A

Dept. Pharmacology, Univ. Leiden, P.O. Box 9502, 2300 RA Leiden, The Netherlands

Adv Exp Med Biol; 136(partA):809-820 1982

41. METABOLISM OF POLYCYCLIC AROMATIC HYDROCARBONS IN PLACENTA.

Juchau MR, Chao ST, Namkung MJ

Dept. Pharmacology, Sch. Medicine, SJ-30, Univ. Washington, Seattle, WA, 98195

Adv Exp Med Biol; 136(partA):555-573 1982

MODIFICATION OF CARCINOGENESIS

42. THE INTESTINAL ENZYMATIC BIOTRANSFORMATION SYSTEM: POTENTIAL ROLE IN PROTECTION FROM COLON CANCER.

Hoensch HP, Hartmann F

Medizinische Universitatsklinik, D-7400 Tubingen, W. Germany

Hepatogastroenterology; 28(4):221-228 1981

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43. THE ONCOGENIC CIRCLE CLOSES.

Rigby PW

Imperial Coll. Science and Technology, London SW7 2BZ, England

Nature; 297(5866):451-453 1982

44. ANALYSIS OF CASES OF HEPATIC CELL CARCINOMA THAT TRANSFORMED FROM VIRAL HEPATITIS.

Ichida F, Homma A, Soga K

Third Dept. Internal Medicine, Niigata Univ. Sch. Medicine, Niigata, Japan

Nippon Rinsho; 40(2):468-477 1982

In JPN

45. ROLE OF VIRUSES IN THE INDUCTION OF PRIMARY INTRACRANIAL TUMORS.

Walsh JW, Zimmer SG, Perdue ML

Div. Neurosurgery, Univ. Kentucky Medical Center, 800 Rose St., Lexington, KY, 40536

Neurosurgery; 10(5):643-662 1982

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46. TRANSLATION OF PHARMACOKINETIC/BIOCHEMICAL DATA INTO RISK ASSESSMENT.

Dietz FK, Reitz RH, Watanabe PG, Gehring PJ

Toxicology Res. Lab., Health and Environmental Sciences, Dow Chemical, 1803 Building, Midland, MI, 48640

Adv Exp Med Biol; 136(partB):1399-1424 1982

47. IN VITRO ASSAYS FOR THE DIFFERENTIATION OF TUMOR PROMOTORS FROM CARCINOGENS AFTER ROUTINE CARCINOGENESIS BIOASSAYS (MEETING ABSTRACT)

Ward JM, Rice JM

Frederick Cancer Research Center, Frederick, MD

Second Annual Meeting of the Society of Environmental Toxicology and Chemistry, November 22-25, 1981, Arlington, Virginia. Society of Environmental Toxicology and Chemistry 150 pp., 1982.

48. ENVIRONMENTAL CARCINOGENS: SELECTED METHODS OF ANALYSIS. VOLUME 4. SOME AROMATIC AMINES AND AZO DYES IN THE GENERAL AND INDUSTRIAL ENVIRONMENT.

Egan H, Fishbein L, O'Neill IK, Castegnaro M, Bartsch H

Lab. Government Chemist, London, England

IARC Sci Publ (40): 347 pp., 1981.

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METABOLIC ACTIVATION OF CARCINOGENS

1. INDUCTION OF COLON MUCOSAL B-GLUCURONIDASE PRODUCTION AS A MECHANISM FOR 1,2-DIMETHYL-HYDRAZINE COLON SPECIFICITY (MEETING ABSTRACT).

Celik C, Lewis DA, Paloini NS, Holyoke ED
Roswell Park Memorial Institute, Buffalo, NY, 14263
Proc Am Assoc Cancer Res; 23:324 1982

Although early studies in germ free rats showed almost complete dependence of dimethylhydrazine (DMH) colon carcinogenesis upon the presence of colon bacteria, no adequate explanation was given for the 20% tumor incidence observed in germ free animals. Bacterial activation of liver microsomal products releasing active proximate carcinogens has been the accepted reason for the exquisite specificity DMH has for the colon. Recent work, including the present study, show the colon mucosa is capable of metabolizing carcinogens and activating conjugated forms metabolized in the liver independent of the intestinal microflora. Mucosal B-glucuronidase production was assayed in coded, scraped mucosa samples from the duodenum/jejunum, ileum, right colon, and left colon of

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normal and DMH treated rats. Normal mucosal B-glucuronidase production was highest in the left colon followed by the right colon, duodenum, and ileum respectively. Enzyme production in the left colon was significantly increased 24 hours after injection of 25mg/kg body weight DMH. No elevation was seen in other mucosal samples. Metabolism of DMH to oxidated forms conjugated to glucuronic acid is well established. Thus, this study offers a possible role for carcinogen induction of a metabolic enzyme in its target tissue. (no Refs)

2. METABOLIC ACTIVATION OF BENZO[A]PYRENE, AFLATOXIN B1, AND DIMETHYLNITROSAMINE BY A HUMAN HEPATOMA CELL LINE.

Huh N, Nemoto N, Utakoji T
Institut fur Zellbiologie (Tumorforschung),, Universitat Essen (GH), Hufelandstrasse 55, 4300 Essen 1, W. Germany
Mutat Res; 94(2):339-348 1982

The frequency of sister-chromatid exchanges (SCE) was measured in normal human fibroblasts (TIG-II) co-cultivated with human hepatoma huH-1 cells to assess the genotoxic effect of activated chemicals aflatoxin B1 (AFB), benzo[a]pyrene (B[a]P), N,N-dimethylnitrosamine (DMN), and 1,2-benzanthracene. When huH-1 cells were treated with 13 uM BA for 24 hr, aryl hydrocarbon hydroxylase activity was induced to 920 picomoles/mg protein/hr, which was approx 24x higher than the basal level. SCE frequency in TIG-II cells changed depending on the inoculum ratio of huH-1 cell to TIG-II cells in the co-culture containing 5 uM AFB. When the inoculum size of huH-1 cells was half that of TIG-II cells, the SCE frequency in TIG-II cells was markedly enhanced over the control level that remained in plateau even in the cultures with larger inocula of huH-1 cells. In the co-culture, the SCE frequency was increased depending on the dose of B(a)P: 0.1 and 12.5 uM of B(a)P induced 7.2 and 10.7 SCE/metaphase, respectively. In the cultures of TIG-II cells only, 0.5 uM of B(a)P showed no significant increase of SCE, while 2.5 and 12.5 uM of B(a)P slightly elevated the SCE frequency over the control level. Treatment with DMN increased the incidence of SCE far more efficiently in the co-cultivation than in cultures of TIG-II cells only. The SCE frequency induced by 0.4 milliM (mM) of DMN in the cultures with huH-1 cells was comparable with that induced by 10 mM of DMN without huH-1 cells. (41 Refs)

3. RELATIONSHIP OF POLYCYCLIC HYDROCARBON (PH) METABOLISM IN RAT MAMMARY CELLS TO TUMOR SUSCEPTIBILITY IN VIVO (MEETING ABSTRACT).

Moore CJ, Bachuber AJ, Gould MM
Department of Human Oncology, University of Wisconsin, Madison, WI, 53792
Proc Am Assoc Cancer Res; 23:318 1982

Since tumor induction rates by PHs vary widely among rat strains, we have confirmed the high susceptibility of Sprague-Dawley (SD) rats to mammary tumorigenesis by 7,12-dimethylbenz(a)anthracene (DMBA) compared to the Long-Evans (LE) strain. We have also found a similar difference between two inbred rat strains, Wistar-Furth (W/Fu) and F344, respectively. Using cultured mammary cells, divided into epithelial or stromal enriched populations, from these 4 strains, we examined DMBA and benzo(a)pyrene (B(a)P) metabolism in relation to in vivo differences in tumor induction rates. B(a)P was converted to water-soluble metabolites at significantly higher rates than DMBA, with a constant ratio of metabolism of the two PHs, in all cell systems tested. The stromal cell populations, which are less susceptible to carcinogenesis in vivo, converted B(a)P and DMBA to water-soluble metabolites 2-4 times faster than the epithelial cell cultures. In contrast, cells from the high susceptibility strains, SD and W/Fu, showed higher levels of water-soluble metabolite production than the less susceptible strains. High-pressure liquid chromatographic analysis of ethyl acetate-extractable *B(a)*P metabolites formed in both mammary cell populations from all 4 strains revealed predominantly 9,10-and some 7,8-dihydrodiol formation, but no major differences by cell type or rat strain. We have measured activation of DMBA and B(a)P to mutagenic metabolites by mammary cells from SD and LE rats, and found similar rates in both strains. (no Refs)

4. CHEMICAL AND ENZYMATIC OXIDATION OF ALKYLATED BENZO[A]PYRENES.

Sullivan PD, Ellis LE, Calle LM, Ocasio IJ
Dept. Chemistry, Ohio Univ., Athens, OH, 45701
Chem Biol Interact; 40(2):177-191 1982

The chemical and enzymatic oxidations of 6-, 7-and 10-methylbenzo[a]pyrenes, 6,10-and 7,10-dimethylbenzo[a]pyrenes and benzo[a]pyrene (BP) itself have been investigated to study the effects of alkyl substitution on the pathways of oxidation. The chemical oxidizing systems employed were Fenton's reagent ($FeSO_4/H_2O_2$); trifluoroacetic acid-hydrogen peroxide (TFA/H_2O_2); thallium tristrifluoroacetate in trifluoroacetic acid (TTFA/TFA) and H_2SO_4. The enzymatic systems were horseradish peroxidase (HRP/H_2O_2) and rat liver microsomes. The oxidations were investigated by electron paramagnetic resonance (EPR) spectroscopy to detect radical intermediates and by high performance liquid chromatography (HPLC) to separate the products. All the compounds studied produced radicals, identified as cationic species, in both H_2SO_4 and TTFA/TFA. In addition the 7-methyl-, 10-methyl- and 7,10-dimethyl-BP's produced 6-oxy radicals in some or all of the remaining oxidizing systems. Both chemically and enzymatically these same three compounds were observed to produce quinones as stable products. Microsomal oxidations gave the broadest range of products exhibiting HPLC peaks in the diol, quinone and phenol regions of the chromatograms, however, there were considerable differences between products from the individual derivatives and those from the parent molecule. 6-Methyl and 6,10-dimethyl-BP's showed no evidence of oxy radical intermediates or quinones under any set of conditions, the 6-substituent effectively blocking this oxidation pathway. The observations are consistent with the expected effects of alkyl substituents at particular positions and indicate that studies such as this one are potentially useful in better understanding oxidation and possible activation pathways of polycyclic aromatic hydrocarbons. (Author abstract) (35 Refs)

5. METABOLISM AND ACTIVATION OF BENZO[A]PYRENE AND BENZO-RING DERIVATIVES DURING PROSTAGLANDIN BIOSYNTHESIS.

Reed GA
Wayne State University, Detroit, MI
Diss Abstr Int [B]; 42(11):4397-B 1982

The cooxygenation of benzo(a)pyrene (BP) and two of its benzo-ring derivatives by ram seminal vesicle preparations has been investigated. The system was first characterized using BP as the substrate. The process was shown to be peroxidatic in nature, utilizing the hydroperoxy compound PGG2 generated in situ by the action of prostaglandin endoperoxide synthetase (PES) on the substrate 5,8,11,14-eicosatetraenoic acid (20:4).

Exogenous PGG2 or 15-hydroperoxyeicosatetraenoic acid could also initiate the cooxygenation of BP, while the hydroxy compound PGH2 was inactive. Non-lipid hydroperoxides possessed very low activities in this system. Heme and certain hemeproteins stimulated cooxygenation of BP. This stimulation was predominantly the result of the inherent peroxidase activity of these agents in that they are themselves able to catalyze hydroperoxide-dependent cooxygenations. 20:4-dependent cooxygenation could be markedly inhibited by indomethacin, a PES inhibitor, supporting the role of PES in cooxygenation. The system was also sensitive to antioxidant inhibition. The isolated products of BP cooxygenation are the 1,6,3,6-, and 6,12-quinones. No intermediates mutagenic to Salmonella typhimurium strains TA98 and TA100 were detected. The BP derivatives, 7,8-dihydroxy-7,8-dihydro-BP (7,8-diol) and 7,8-dihydro BP (H2BP) were both activated by cooxygenation to intermediates highly mutagenic to TA98 and TA100. (no Refs)

6. METABOLISM OF BENZO(A)PYRENE AND AFLATOXIN B1 IN CULTURED HUMAN AND ANIMAL MODEL BLADDER AND TRACHEOBRONCHIAL TISSUES (MEETING ABSTRACT).

Daniel FB, Stoner GD, Sandwisch DW, Schenck KM, Schut HA
Health Effects Research Laboratory, U.S. Environmental Protection Agency, Cincinnati, OH, 45268
Proc Am Assoc Cancer Res; 23:327 1982

The metabolism, DNA binding and -adduct formation of benzo(a)pyrene (BP) and aflatoxin B1 (AFB) in human and animal species (monkey, rat, hamster, dog) has been compared using cultured explants of bladder and tracheobronchial tissues. Human bladder and bronchial specimens obtained from autopsies and animal tissues obtained from sacrifice were cultured as explants in serum-free medium. The cultures were rocked to permit intermittent tissue exposure to medium and atmosphere. After three days, the explants were exposed for 24 hrs to either [3H]BP or [3H]AFB (10-6M each). Epithelial cell DNA was isolated by hydroxyapatite chromatography and, after hydrolysis of the DNA, high pressure liquid chromatography (HPLC) was used to identify the carcinogen-DNA adducts. Among the species, BP binding to bladder cell DNA was highest in the human and lowest in the rat and that to tracheobronchial DNA was highest in the hamster and lowest in the dog. For both bladder and tracheobronchial tissues, AFB binding to DNA was highest in the hamster and lowest in the human. In all tissues, 2,3-dihydro-2-(N7-guanyl)-3-hydroxy-AFB and 7,8,9-trihydroxy-10(-N2-deoxyguanosine)-BP adducts were identified after incubation with AFB and BP, respectively. The profile of BP metabolites in the medium (analyzed by HPLC) from all tissues was qualitatively similar. (no Refs)

7. CHARACTERISTICS OF MICROSOMAL REDUCTION OF BENZO[A]PYRENE 4,5-OXIDE.

Wrighton SA, Fahl WE, Shinnick FL, Jefcoate CR
(c/o Jefcoate) Dept. Pharmacology, Univ. Wisconsin Medical Sch., Madison, WI, 53706
Chem Biol Interact; 40(3):345-356 1982

NADPH-reduction of benzo[a]pyrene 4,5-oxide (BP-4,5-oxide) to BP required four components from rat liver: cytochrome P-450, NADPH cytochrome P-450 reductase, phosphatidylcholine and a soluble, heat-sensitive factor which was present in 105,000 x g supernatant and was also released from microsomes by sonication. The requirement for this factor contrasts with recently reported results from Sugiura et al. Oxide-reduction was 40x faster under anaerobic conditions, but oxygen did not affect the stimulation factor. This stimulation was highest (x15) at low concentrations of microsomal protein (less than 0.1 mg/ml) and was almost absent at high concentrations of microsomal protein (greater than 1 mg/ml). Oxide-reduction activity was proportional to microsomal protein concentration in the presence of added 105,000 x g supernatant, but for microsomes alone (greater than 0.1 mg/ml) exhibited a parallel plot with an intercept at 0.08 mg/ml microsomal protein. Stimulation was highest at high concentrations of BP-4,5-oxide and a linear plot of V1 vs. [BP-4,5-oxide](1) was only obtained in the presence of 105,000 x g supernatant (Km = 3uM, Vmax = 3.3 nmol/mg/min). Microsomal hydration of BP-4,5-oxide (inhibited in reductase assays) was unaffected by 105,000 x g supernatant, suggesting that stimulation of oxide-reduction did not derive from solubilization of BP-4,5-oxide. Stimulation was observed in the initial rate of reaction and was independent of incubation time. Inhibition of lipid peroxidation, removal of peroxides and deoxygenation were all excluded as explanations of the stimulatory effect. (Author abstract) (18 Refs)

8. TIME COURSE OF METABOLISM OF BENZO[E]PYRENE BY HAMSTER EMBRYO CELLS AND THE EFFECT OF CHEMICAL MODIFIERS.

MacLeod MC, Mansfield BK, Selkirk JK
Biology Div., Oak Ridge Natl. Lab., Oak Ridge, TN, 37830
Chem Biol Interact; 40(3):275-285 1982

In cultures of hamster embryo cells, benzo[a]pyrene (B[a]P) is metabolized primarily in the bay region. In contrast, little or no bay region metabolism of the noncarcinogenic isomer benzo[e]pyrene (B[e]P) could be detected during 12-96-h incubations of hamster embryo cells with 4uM [3H]B[e]P. The upper limit to 9,10-dihydro-9,10-dihydroxy-benzo[e]pyrene formation is about 0.2% of the ethyl acetate-soluble metabolites (less than 0.1% of the total metabolites). The major identified metabolites of B[e]P were 4,5-dihydro-4,5-dihydroxy benzo[e]pyrene and the glucuronide conjugates of 3-OH-benzo[e]pyrene and 4,5-dihydro-4,5-dihydroxy B[e]P. Simultaneous treatment of cells with either B[a]P or 7,8-benzoflavone (BF) did not induce bay region metabolism of [3H]B[e]P. (Author abstract) (27 Refs)

9. METABOLISM OF 6-NITROBENZO(A)PYRENE BY HAMSTER EMBRYO CELLS AND RAT LIVER MICROSOMES (MEETING ABSTRACT).

Tong S, Selkirk JK
University of Tennessee-Oak Ridge Graduate School of Biomedical Sciences, Oak Ridge, TN, 37830
Proc Am Assoc Cancer Res; 23:312 1982

Nitrosarenes are formed during combustion of diesel fuel. Several of these compounds are known mutagens in short-term assay and are therefore suspect as presenting a potential human risk. The metabolism of a suspected environmental contaminant, 6-nitrobenzo(a)pyrene, was studied employing hamster embryonic fibroblasts and hepatic microsomes from 3-methylcholanthrene pretreated rats to compare intact cell metabolism against cell-free systems routinely used in short-term mutagenic assays. Organic solvent-soluble metabolites were separated by high-pressure liquid chromatography. Incubation of 6-nitrobenzo(a)pyrene with hamster embryo cells gave rise to both organic and water-soluble metabolites. When ethyl acetate extract of the extracellular medium was analyzed, a major peak at the dihydroxy region was detected 24 hr after introduction of substrate to cell culture. Small amounts of a phenolic product was also obtained at this time point. Subsequent treatment of remaining aqueous phase with beta-glucuronidase, however, indicated that the majority of the phenol produced had readily been converted to water-soluble glucuronide conjugates. Intracellular metabolites of 6-nitrobenzo(a)pyrene were also detected and comprised mainly of phenolic and dihydroxy products. As a comparison to cellular metabolism, hepatic microsomes were incubated with 6-nitrobenzo(a)pyrene in the presence of NADPH. Microsomal metabolism resulted in the production of one major phenolic metabolite, which was previously found to be conjugated in the cellular system, with minor dihydroxy and quinone products. (no Refs)

10. IN VITRO METABOLISM OF 12-METHYLBENZ(A)ANTHRACENE: EFFECT OF THE METHYL GROUP ON THE STEREOCHEMISTRY OF A 5,6-DIHYDRODIOL METABOLITE.

Fu PP, Chou MW, Yang SK

Natl. Center for Toxicological Res., Jefferson, AR, 72079

Biochem Biophys Res Commun; 106(3):940-946 1982

Metabolism of 12-methylbenz(a)anthracene (MBA) by rat liver microsomes formed a (-)trans-5,6-dihydrodiol with S,S absolute stereochemistry as the predominant enantiomer. When benz(a)anthracene (BA) was incubated under similar conditions, (+)BA trans-5R,6R-dihydrodiol was the major enantiomer formed. Thus, a methyl substituent of a polycyclic aromatic hydrocarbon may alter the stereoselective preference of the rat liver microsomal drug-metabolizing enzyme system toward the substrate molecule in the formation of a dihydrodiol metabolite at an unsubstituted aromatic double bond. (16 Refs)

11. XANTHINE OXIDASE-CATALYZED REDUCTION OF 1-NITROPYRENE TO A POTENTIALLY MUTAGENIC DNA-BINDING SPECIES (MEETING ABSTRACT).

Howard PC, Beland FA, Evans FE, Heflich RH

The National Center for Toxicological Research, Jefferson, AR, 72079

Proc Am Assoc Cancer Res; 23:242 1982

Since metabolic reduction of this nitroarene would be expected to yield a reactive N-hydroxy derivative, we have examined the ability of a mammalian nitroreductase, xanthine oxidase, to catalyze the binding of nitropyrene to DNA. Incubation of 20 uM [4,5,9, 10-^{3}H]1-nitropyrene (117 mCi/mmol), 3.7 mM hypoxanthine, 0.5 U/ml xanthine oxidase and 2 mg/ml calf thymus DNA gave a linear increase in DNA adduct formation over a 60 min period. Covalent binding was inhibited by allopurinol, a xanthine oxidase inhibitor, and by heat denaturation of the enzyme. Nitropyrene-DNA binding also occurred when hypoxanthine was replaced with xanthine, albeit at a lower level. Enzymatic hydrolysis of the DNA and subsequent analysis by high pressure liquid chromatography indicated the presence of one major nitropyrene-deoxyribonucleoside adduct. The product was characterized by electron impact in-beam desorption mass spectrometry and 500 MHz 1H-nuclear magnetic resonance spectroscopy as N-(deoxyguanosin-8-yl)-1-aminopyrene. When Salmonella typhimurium strain TA1538 was incubated with 3H-1-nitropyrene in suspension culture for 6 hr, a time-dependent linear increase in total macromolecular binding and reversion frequency was observed. Bacterial DNA was isolated by hydroxylapatite chromatography and enzymatically hydrolyzed to nucleosides, to yield one major adduct with a retention time identical to N-(deoxyguanosin-8-yl)-1-aminopyrene. (no Refs)

12. THE CO-OXIDATION OF 2-AMINOFLUORENE DURING PROSTAGLANDIN BIOSYNTHESIS IN RAM SEMINAL VESICLE MICROSOMES (MEETING ABSTRACT).

Boyd JA, Eling TE

National Institute of Environmental Health Sciences, Research Triangle Park, NC, 27709

Proc Am Assoc Cancer Res; 23:78 1982

The metabolism of the chemical carcinogen 2-aminofluorene (2-AF) during prostaglandin biosynthesis, using ram seminal vesicle microsomes as a source of prostaglandin endoperoxide synthetase (PES), was examined. 2-AF inhibited prostaglandin biosynthesis in a dose-dependent manner, as well as the peroxidatic co-oxidation of phenylbutazone, suggesting that 2-AF is both an inhibitor of PES and a reducing co-factor for the hydroperoxidase activity of PES. At a concentration of 100 uM, 2-AF was co-oxidized during prostaglandin biosynthesis to 2-nitrofluorene and 2,2'-bisazoxyfluorene, both of which were isolated and identified by co-chromatography and mass spectrometry. The formation of 2,2'-bis-azoxyfluorene indicated the formation of N-OH-2-AF as well. This 2-AF metabolism was dependent on the presence of the PES substrate arachidonic acid, inhibited by the PES inhibitor indomethacin, and was not observed using heat denatured microsomal protein. Preliminary data suggest that N-OH-2-AF is also a substrate for PES, and is metabolized to 2-nitrofluorene and 2,2'-bisazoxyfluorene as well. In addition, 2-AF was metabolized to a mutagenic metabolite(s), as measured by using RSV as an activating system in the Ames test. In summary, the above data indicate that the co-oxidation of 2-AF during prostaglandin biosynthesis in vitro results in the formation of N-OH-2-AF, the presumed ultimate carcinogenic metabolite of 2-AF and 2-acetylaminofluorene. (no Refs)

13. MICROSOMAL METABOLISM OF THE CARCINOGEN, N-2-FLUORENYLACETAMIDE (2-FAA), IN THE RAT MAMMARY GLAND (MEETING ABSTRACT).

Ryzewski CN, Malejka-Giganti D, Polovina M

Department of Laboratory Medicine and Pathology, University of Minnesota, Minneapolis, MN, 55455

Proc Am Assoc Cancer Res; 23:308 1982

Studies of metabolism of 2-FAA in its extrahepatic target were made possible with our new high performance liquid chromatographic method which overcomes previous difficulties in quantitative elution of N-hydroxy-2-FAA and concomitant separation of 8 other metabolites of 2-FAA. Peak detection is by UV absorbance and quantitation is by peak area determination relative to standard curves. We have determined the products which form during incubation of 2-FAA with mammary gland microsomes (MGM) of lactating rats treated with corn oil (control) and 3-methylcholanthrene or beta naphthoflavone. These compounds induced cytochrome P1-450 in MGM and hepatic microsomes (HM). Overall metabolism, indicated by decreases in substrate, was slower in MGM than in HM for equivalent amounts of microsomal protein from rats treated with the inducers. MGM from control rats were capable only of hydroxylation to 9-, 5-and 3-hydroxy-2-FAA. MGM from induced rats had enhanced capacities to hydroxylate to 5-and 3-hydroxy-2-FAA and had the capacities to hydroxylate to 7-hydroxy-2-FAA and most importantly to N-hydroxy-2-FAA, the proximate mammary gland carcinogen. The capacity of MGM of induced rats to convert 2-FAA to N-hydroxy-2-FAA may be of significance in tumorigenesis not only in the mammary gland but in suckling rats as well. (no Refs)

14. METABOLIC ACTIVATION OF N-HYDROXY-N-ACYL-2-AMINOFLUORENES BY RAT ZYMBAL'S GLAND (MEETING ABSTRACT).

Allaben WT, Weis CC
National Center for Toxicological Research, Jefferson, AR, 72079
Proc Am Assoc Cancer Res; 23:321 1982

A target tissue for many carcinogenic aromatic amines in the rat is the Zymbal's gland. Because of recent findings that the N-propionyl derivative of N-hydroxy-2-aminofluorene (NP) was a potent carcinogen in this tissue, we have compared the in vitro metabolism of NP to the less carcinogenic N-acetyl (NA) and N-formyl (NF) derivatives. The Zymbal's glands from S/D rats were removed, homogenized and fractionated by centrifugation into the 9000 x g supernatant (S9), cytosol, and microsomes N,O-Acyltransferase (AT) (assayed by tRNA:fluorenyl adduct formation) and deacylase (assayed by N-hydroxy-2-aminofluorene formation) activities were determined using these fractions. The cytosol was further fractionated by gel-filtration. AT assays showed activities as follow: for S9, NF greater than NP greater than NA; for cytosol, NF greater than NP greater than NA; and for microsomes, NF much greater than NA greater than NP. Paraoxon inhibited adduct formation catalyzed by the cytosol fractions for NF, and by microsomes for NF, NP, and NA. In contrast, deacylase assays were as follows: S9, NP greater than NA much greater than NF; cytosol, no activity; and microsomes, NP much greater than NA much greater than NF. All deacylase reactions were paraoxon-sensitive. Gel-filtration chromatography of cytosol demonstrated two AT's: an early eluting fraction with high specificity for NF; and a later eluting fraction exhibiting activity for NP. Relative Zymbal's gland AT activity, compared to liver AT activity, is about 0.03 for NA, 0.3 for NP and 1 for NF. Zymbal's gland deacylase activity, compared to liver deacylase activity, is about 2x for NA and about 3x for NP. Deacylation appears to be the major metabolic pathway in Zymbal's gland homogenates for NP and NA. Moreover, deacylase activity corrrelates with the tumor incidence observed in Zymbal's gland (NP greater than NA greater than NF). (no Refs)

15. ACTIVATION OF N-OH-AAF BY RAT MAMMARY GLAND PARENCHYMAL CELLS VIA A LIPOXYGENASE-PEROXIDASE ROUTE (MEETING ABSTRACT).

Wong PK, Floyd RA
Oklahoma Medical Research Foundation, Oklahoma City, OK, 73104
Proc Am Assoc Cancer Res; 23:323 1982

The proximate carcinogen, N-hydroxy-2-acetylamino-fluorene (N-OH-AAF) was found to be metabolized into 2-nitrosofluorene (NOF) and N-acetoxy-2-acetylaminofluorene (N-OAc-AAF) by rat mammary parenchymal cells through a peroxidative mechanism. The detection of N-OAc-AAF and NOF as end products by high pressure liquid chromatography (HPLC), the presence of nitroxyl free radical as indicated by electron spin resonance spectroscopy (ESR) and the inhibitory actions of peroxidase inhibitors such as ascorbate and p-aminophenol strongly suggest that peroxidative oxidation is the major route operating in such a system and that neither the acyltransferase nor deacylase route occurs to any appreciable extent. Ram seminal vesicle microsomes also activate N-OH-AAF to NOF. Unlike the prostaglandin synthetase, mammary cell enzymes are not affected by indomethacin or aspirin while lipoxygenase inhibitors, 5,8,11,14-eicosatetraynoic acid (ETYA), gossypol and Fe(III) chelators such as deferoxamine inhibit the cell activity. Externally added arachidonate enhances N-OH-AAF activation. The hydroperoxides generated from exogenous and endogenous arachidonate by the lipoxygenase pathway is believed to be the substrate for the peroxidase activation mechanism. Mammary cells isolated from animals on selenium-supplemented diet are less active than cells from animals on selenium-deficient diet. As selenium was known to inhibit tumor formation on experimental animals, lipoxygenase and peroxidase activities of mammary gland cells appear to be related to mammary carcinogenesis. (no Refs)

16. METABOLIC ACTIVATION OF BENZO(B)FLUORANTHENE IN MOUSE SKIN (MEETING ABSTRACT).

LaVoie EJ, Amin S, Juchatz A, Hecht SS, Hoffman D
American Health Foundation, Valhalla, NY, 10595
Proc Am Assoc Cancer Res; 23:332 1982

Benzo(b)fluoranthene (B[b]F) is a ubiquitous carcinogenic polynuclear aromatic hydrocarbon. The metabolic activation of B[b]F in mouse skin was studied using two approaches: characterization of B[b]F-DNA adducts formed in vivo and tumorigenicity assays of monofluorinated derivatives of B[b]F. 3H-B[b]F (400 uCi, 99 ug/mouse) was applied to mouse skin, after 24 hrs DNA was isolated from the treated epidermis, and enzymatically hydrolyzed to deoxyribonucleosides. Chromatography on Sephadex LH-20 revealed five bands (A-E) of radioactivity (eluting between 480-780 ml). These bands had the following percentages of radioactivity: A (12%), B (19%), C (32%), D(32%), and E (6%). Band B corresponded in elution volume to the major reaction product of B[b]F-9,10-diol-11,12-epoxide with calf thymus DNA in vitro. Approx 32% of B was also found to coelute on high performance liquid chromatography with this synthetic bay region dihydrodiol epoxide-nucleoside marker. These results suggest that the DNA adduct from B[b]F-9,10-diol-11,12-epoxide represents a minor fraction of the DNA adducts of B[b]F formed in mouse skin. To investigate which positions of B[b]F are associated with its activation, 7-flouroB[b]F, 9-flouroB[b]F, and 11-fluoroB[b]F were synthesized. Metabolism studies with rat liver 9000 x g supernatant indicated that fluorine blocked dihydrodiol and phenol formation at the carbon with the fluorine atom. Each fluorinated compound was tested for tumor-initiating activity at initiating doses of 30 and 100 ug. (no Refs)

17. ESOPHAGEAL AND HEPATIC MICROSOMAL METABOLISM OF N-NITROSOMETHYLBENZYLAMINE AND N-NITROSODIMETHYLAMINE IN THE RAT.

Labuc GE, Archer MC
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Cancer Res; 42(8):3181-3186 1982

The metabolism of the rat esophageal carcinogen N-nitrosomethylbenzylamine (NMBzA) was studied using microsomes prepared from liver and esophageal mucosa of untreated male Sprague-Dawley rats. NMBzA was extensively metabolized to benzaldehyde, benzyl alcohol, and formaldehyde by hepatic microsomes. The rate of metabolism at the benzyl moiety was 10-fold higher than that at the methyl moiety. Mucosal microsomes metabolized NMBzA to benzaldehyde and formaldehyde at rates one-fifth and one-sixtieth of those in the liver, respectively; benzyl alcohol formation was undetectable. Esophageal metabolism of NMBzA was exclusively located in the mucosa, preferentially in the microsomal fraction, was reduced nicotinamide adenine dinucleotide phosphate dependent, and was inhibited CO and 2-diethylaminoethyl-2,2-diphenylvalerate. A low level of cytochrome P-450 was detected in the mucosal microsomes. Whereas hepatic metabolism of NMBzA was inducible by phenobarbitone pretreatment, mucosal metabolism was not altered by either phenobarbitone or 3-methylcholanthrene pretreatment. The hepatocarcinogen N-nitrosodimethylamine was extensively metabolized by hepatic microsomes to formaldehyde, but demethylation was not detected in the microsomes from esophageal mucosa, a nontarget tissue. The results indicate that rat esophageal mucosa contains an enzyme system which metabolized NMBzA at a high rate and exhibits properties typical of cytochrome P-450. This enzyme may play a role in determining which compounds induce tumors in rat esophagus. (Author abstract) (26 Refs)

18. STUDIES ON THE METABOLIC ACTIVATION OF BENZIDINE BY ISOLATED RAT HEPATOCYTES.

Brouns RM, Bos RP, Van Doorn R, Henderson PT
Inst. Pharmacology and Toxicology, Univ. Nijmegen, Nijmegen, The Netherlands
Toxicology; 23(2/3):235-247 1982

Isolated parenchymal liver cells of adult male Wistar rats were exposed to benzidine and the mutagenic activity of the resulting metabolite in the Ames Salmonella typhimurium assay was determined. Induction of DNA repair in the liver cells themselves was also studied. Intact rat liver cells metabolized the benzidine to more mutagenic derivatives than did the 9,000-g supernatant from the hepatocytes. Harmine (an inhibitor of N-acetyltransferase), markedly reduced the mutagenicity of derivatives produced, whereas, salicylamide (an inhibitor of sulfotransferase), had no influence. A time-dependent enhancement of mutagenicity in the Ames assay was observed when benzidine was pre-incubated with intact rat liver cells before being exposed to the 9,000 g supernatant; revertant colonies attained levels 4x those observed when only untreated supernatant was used. Exposure of liver cells to benzidine resulted in a concentration-dependent increase in 3H-thymidine incorporation up to approx 10(-5) M benzidine. Decreasing the N-acetylation and sulfation capacity of the liver cells with harmine and salicylamide, respectively, decreased the incorporation of 3H-thymidine to the level observed in the absence of benzidine, suggesting that both reactions are involved in the generation of reactive metabolites in the liver cell. Evidence was found for an N-acylated metabolite that, when activated by the 9,000 g supernatant, was considerably more mutagenic than benzidine itself. A tentative reaction scheme is presented. (22 Refs)

19. METABOLIC PATHWAYS FOR THE CARCINOGEN, BENZIDINE, WHICH RESULT IN COVALENT BINDING TO DNA (MEETING ABSTRACT).

Frederick CB, Martin CN, Weis CC, Kadlubar FF
The National Center for Toxicological Research, Jefferson, AR, 72709
Proc Am Assoc Cancer Res; 23:322 1982

Benzidine (BZ), a urinary bladder carcinogen in humans and dogs, induces hepatic tumors in mice and rats. In recent studies, we identified a single carcinogen-DNA adduct, N-(deoxyguanosin-8-yl)-N'-acetyl-BZ, in mouse and rat liver following an ip dose of BZ or N-acetylbenzidine (N-ABZ). N,N'-Diacetylbenzidine (DABZ) did not produce a detectable level of DNA binding. To determine which metabolic activation pathways result in DNA binding in vivo, we examined the N-acetylation, N-hydroxylation, N-deacetylation, and O-esterfication of BZ and its derivatives in vitro using rat liver subcellular fractions. N-ABZ, a known metabolite of BZ, was preferentially oxidized on the amide nitrogen by NADPH-fortified microsomes to yield N-hydroxy-N-ABZ. N'-Hydroxy-N-ABZ was not detected. N-Hydroxy-N-ABZ was then N-acetylated by liver cytosol and acetyl CoA to give N-hydroxy-DABZ. N-Hydroxy-DABZ was further selectively deacetylated by hepatic microsomes to yield N'-hydroxy-N-ABZ. Both of these were substrates for purified hepatic N,O-acyl-transferase, resulting in intra- and intermolecular acyl transfer, respectively, and subsequent covalent binding to added DNA. Enzymatic hydrolysis of the DNA and high pressure liquid chromatography yielded the identical C-8-deoxy-guanosine adduct found in vivo. Similar results, albeit at lower levels of binding, were obtained by reaction of N'-hydroxy-N-ABZ directly with DNA. Thus, these data suggest that N'-hydroxy-N-ABZ and N-hydroxy-DABZ are proximate carcinogenic metabolites of BZ in the rat. (no Refs)

20. ELECTRON SPIN RESONANCE STUDY ON THE METABOLISM OF 2-NAPHTHYLAMINE AND 1-NAPHTHYLAMINE IN RAT LIVER MICROSOMES.

Nakayama T, Kimura T, Kodama M, Nagata C
Biophysics Div., Natl. Cancer Center Res. Inst., Tsukiji 5-1-1, Chuo-ku, Tokyo 104, Japan
Gan; 73(3):382-390 1982

Incubation of 2-naphthylamine (2-NA) with rat liver microsomes fortified with NADPH resulted in the formation of two types of free radicals which were identified as being due to N-hydroxy-2-naphthylamine and 2-amino-l-naphthol. The former radical was shown to be oxidized further to 2-nitrosonaphthalene radical. Compared with the case of the constitutive microsomes, the amount of the free radicals increased progressively on using the microsomes from methylcholanthrene (MC)-induced or phenobarbital (PB)-induced rats. On the other hand, the amount of the free radical formed from 1-naphthylamine (1-NA) was much less than that from 2-NA, so that the radical structure was not identified unambiguously. The enzymes involved in this case were not induced by either MC or PB. Thus, from the viewpoint of free radical formation, the metabolic patterns of 2-NA and 1-NA are quite different and such different behavior might be correlated with the distinct difference in their carcinogenicities. From the inhibitory effects of carbon monoxide, SKF-525A, alpha-naphthoflavone and 1-(1-naphthyl)-2-thiourea on the free radical formation, it was concluded that both mixed function oxidases (cytochrome P-450s) and mixed function amine oxidase (dimethylaniline monoxygenase) are involved in the metabolism of 2-NA. (Author abstract) (31 Refs)

21. SPECIES-SPECIFIC ACTIVATION OF PHENACETIN INTO BACTERIAL MUTAGENS BY HAMSTER LIVER ENZYMES AND IDENTIFICATION OF N-HYDROXYPHENACETIN O-GLUCURONIDE AS A PROMUTAGEN IN THE URINE.

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Cancer Res; 42(8):3201-3208 1982

Phenacetin was mutagenic in Salmonella typhimurium TA100 in plate assays when liver fractions from Aroclor-treated hamsters, but not rats, were used. Its known or putative metabolites were synthesized; of these, N-hydroxyphenacetin and N-acetoxyphenacetin were found to be mutagenic in liquid and plate assays, both requiring activation by liver fractions from Aroclor-treated hamsters. 2-Hydroxyphenacetin and 2-acetoxyphenacetin were nonmutagenic. N-Hydroxyphenetidine (the deacetylated metabolite of phenacetin) and p-nitrosophenetole were the only products that were found to be mutagenic per se when assayed under N2 in either Salmonella TA100 and TA100 NR (nitroreductase-deficient) strains. Phenacetin was administered to male BDVI rats and Syrian golden hamsters, and its urinary metabolites were deconjugated with beta-glucuronidase:arylsulfatase. After reactivation by hamster liver fractions, mutagenicity was demonstrated in S typhimurium TA100 with urine from phenacetin-treated hamsters, but not with that from rats. After treatment with deconjugating enzymes, N-hydroxyphenacetin was isolated from hamster urine by high-performance liquid chromatography and identified by mass spectral analysis. The data support the conclusions that (a) N-hydroxyphenacetin is a proximate mutagenic metabolite of phenacetin which, after N-deacetylation, is responsible for the mutagenicity observed in vitro and in the urine of hamsters and (b) the higher yield of N-hydroxyphenacetin that is formed in the liver of hamsters as compared to rats explains the pronounced species-specific activation of phenacetin into bacterial mutagens. (Author abstract) (59 Refs)

22. RAT LIVER MICROSOMAL METABOLITES OF 7-METHYLBENZ[C]-ACRIDINE.

Ireland CM, Cheung HT, Ryan AJ, Holder GM
Dept. Pharmacy, Univ. Sydney, NSW 2006, Australia
Chem Biol Interact; 40(3):305-318 1982

The metabolism of the weak carcinogen 7-methylbenz[c]acridine (7MBAC) was examined in rat liver microsomes from 3-methylcholanthrene (MC)-induced animals by the use of mixed 14C- and 2H-labeled substrate. The three metabolites identified by spectroscopic and chromatographic examination were 7-OHMBAC and two dihydrodiols. The dihydrodiols were assigned structures consistent with attack on the 8,9-and 5,6-or K-region of the aromatic system. (Author abstract) (32 Refs)

23. COMPARISON OF THE MUTAGENICITY AND TERATOGENICITY OF CYCLOPHOSPHAMIDE AND ITS ACTIVE METABOLITES, 4-HYDROXYCYCLOPHOSPHAMIDE, PHOSPHORAMIDE MUSTARD, AND ACROLEIN.

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Cancer Res; 42(8):3016-3021 1982

Cyclophosphamide must be metabolically activated to have max mutagenic or teratogenic activity. The first step in this activation is hydroxylation to 4-hydroxycyclophosphamide; this metabolite breaks down to form two cytotoxic metabolites, phosphoramide mustard and acrolein. In this report, the mutagenicity and teratogenicity of cyclophosphamide, 4-hydroperoxycyclophosphamide (which forms 4-hydroxycyclophosphamide spontaneously in solution), phosphoramide mustard, and acrolein were compared. The activation of cyclophosphamide to mutagenic metabolites was dependent on the presence of liver microsomes and reduced nicotinamide adenine dinucleotide phosphate while both phosphoramide mustard and 4-hydroperoxycyclophosphamide were mutagenic without activation, with the latter being the most potent. The third metabolite, acrolein, was bacteriotoxic at low concentrations; it was not mutagenic in the absence and only very weakly mutagenic in the presence of liver microsomes. All four compounds tested were teratogenic. The malformations produced by cyclophosphamide, 4-hydroperoxycyclophosphamide, and acrolein included edema, hydrocephaly, open eyes, cleft palate, micrognathia, omphalocele, bent tail, and forelimb and hindlimb defects, whereas phosphoramide mustard produced only hydrocephaly and tail, forelimb, and hindlimb defects. 4-Hydroperoxycyclophosphamide and its breakdown product, acrolein, were more potent as teratogens than either cyclophosphamide or phosphoramide mustard. cyclophosphamide produced malformations in both the injected and contralateral uninjected fetuses while the other three compounds all produced malformations only in the injected fetuses. Thus, the site of activation of cyclophosphamide to a teratogen is probably maternal. Because acrolein plays a major role in the teratogenicity of cyclophosphamide but is only weakly, if at all, mutagenic, the teratogenicity and mutagenicity of metabolites of this drug are dissociable. (41 Refs)

24. ACTIVATION OF TRP-P-1 AND TRP-P-2 IN VITRO AND IN VIVO.

Dolara P, Caderni G, Benetti D
Inst. Pharmacology and Toxicology, Univ. Florence, Florence, Italy
Nutr Cancer; 3(3):168-171 1982

Isolated perfused livers were not able to activate the promutagens Trp-P-1 and Trp-P-2 to their genotoxic metabolites. On the contrary, inherently active mutagenic compounds were detected in the bile of living rats to which Trp-P-1 and Trp-P-2 had been administered intravenously. The excretion of active mutagens through the bile may explain the tumorigenic effect that these compounds exert on the liver during chronic feeding experiments. (Author abstract) (8 Refs)

25. STUDIES ON THE O-DEMETHYLATION OF MISONIDAZOLE BY RAT LIVER MICROSOMES.

Shoemaker DD, McManus ME, Hoerauf R, Strong JM
Investigational Drug Branch, NCI, NIH, Landow Building, Room 4C19, 7910 Woodmont Ave., Bethesda, MD, 20814
Cancer Treat Rep; 66(6):1343-1347 1982

The role of rat liver microsomes in the O-demethylation of misonidazole to desmethylmisonidazole was studied. The rate of the microsomal-dependent formation of desmethylmisonidazole was linear up to a protein concentration of 2 mg/ml and over a 10-min interval. The metabolism was optimal in a system comprised of microsomes, O2, and NADPH. Metabolism in incubation mixtures continuously flushed with N2 was inhibited by 78%. The O-demethylase activity was competitively inhibited by the addition of SKF 525-A, with a Ki of approx 1 x 10(-5) M. The Km and Vmax values of normal microsomes were 1.87 +-0.30 mM and 413 +-14 pmols/minute/mg of microsomal protein, respectively. Pretreatment of rats with phenobarbital for 7 days prior to preparation of the microsomes resulted in no significant change in the Km, but the Vmax was considerably increased to 1,033 +-203 pmols/minute/mg of microsomal protein. The results demonstrate that the O-demethylation of misonidazole is mediated by cytochrome P-450. (Author abstract) (16 Refs)

26. ORGAN CULTURES FOR THE STUDY OF CHEMICAL CARCINOGENICITY (MEETING ABSTRACT).

Reiss B, Williams GM
American Health Foundation, Naylor Dana Institute for Disease Prevention, Valhalla, NY, 10595
In Vitro; 18(3,part2):289 1982

An in vitro system using organized tissue provides several advantages over in vivo and cell culture systems for the study of carcinogenesis; intercellular and intracellular processes as well as tissue interaction can be investigated in the precisely controlled environment of an organ culture system. Currently, several variations of basic organ culture methodologies for adult mammalian organs (colon, esophagus, trachea, skin, mammary gland, lung etc) produce long-term preservation of the epithelium with minimal histological or functional deviations from the normal in vitro condition. Several aspects of chemical carcinogenesis are under study in organ culture systems. The metabolism of carcinogens is being investigated directly, by examining the formation of metabolites in organ culture and, indirectly, by observing the acute molecular effects produced by reactive metabolites on the cultured tissue. Using these two parameters the metabolism of organ selective carcinogens has been documented in cultures of colon and esophagus. (no Refs)

OTHER METABOLISM OF CARCINOGENS

27. DIMETHYLNITROSAMINE ADDUCTS EXCRETED IN RAT URINE.

Hemminki K, Vainio H
Dept. Industrial Hygiene and Toxicology, Inst. Occupational Health, SF-00290 Helsinki 29, Finland
Adv Exp Med Biol; 136B:1149-1156 1982

Urinary excretion products found after the administration of dimethylnitrosamine (DMN) to Wistar rats were detected with an assay involving nucleic acids and protein. Rats received 25 uCi of 14C-DMN and urine was collected daily. Three main peaks of radioactivity were detected in each urine sample. The peaks were then analyzed with thinlayer and high pressure chromatography, a muBondaPak C18 column, and dissociation constants and relative turnover rates were determined. Fraction I was thought to consist of S-methylcysteine; its approx half-life was 1.7 days, slightly shorter than that of methylated proteins in vivo. Urinary S-methylcysteine may be derived from the degradation products of methylated proteins and/or glutathione. Fraction II could not be identified; its properties suggested that it was probably not a methylated degradation product of nucleic acids or protein. Fraction III was identified as 7-methylguanine, with an approx half-life of 2.4 days. 7-Methylguanine may be derived from methylated RNA and DNA. These findings illustrate the usefulness of the study of urinary adducts of carcinogens for monitoring a known chemical exposure and providing information about an unknown exposure. (13 Refs)

28. ESOPHAGEAL AND HEPATIC MICROSOMAL METABOLISM OF N-NITROSO-METHYLBENZYLAMINE (NMBZA) AND N-NITROSODIMETHYLAMINE (NDMA) IN THE RAT (MEETING ABSTRACT).

Labuc GE, Archer MC
Ontario Cancer Institute, Toronto, Ontario, M4X 1K9, Canada
Proc Am Assoc Cancer Res; 23:311 1982

The metabolism of the rat esophageal carcinogen, NMBzA, and the rat hepatocarcinogen, NDMA, was compared using microsomes prepared from the respective target and non-target tissues. Each compound (5mM) was incubated with microsomes and an NADPH generating system. Hepatic microsomes metabolized NDMA to formaldehyde (dimedone assay), and NMBzA to formaldehyde, benzaldehyde and benzyl alcohol (high performance liquid chromatography assay). The overall rates of metabolism of the nitrosamines were similar. However, hepatic microsomal metabolism of NMBzA at the methylene carbon proceeded at 10 times the rate of metabolism at the methyl carbon. In contrast, microsomes from esophageal mucosa metabolized NMBzA to benzaldelyde and formaldehyde only; benzyl alcohol formation was not detected. The rate of benzaldehyde formation was 100 times that of formaldehyde. The esophageal metabolizing system was exclusively located in the mucosa, and preferentially in the microsomal subcellular fraction. The system exhibited properties typical of a cytochrome P-450 pathway, being NADPH dependent, and being inhibited by CO and SKF 525-A, but was unaltered by either phenobarbitone or 3-methylcholanthrene pretreatment. The results indicate that hepatic microsomes metabolize both compounds to a similar extent. In contrast, esophageal microsomes preferentially metabolize the esophageal carcinogen, NMBzA, and the metabolizing system may thus play a role in determining which chemicals induce tumors in the rat esophagus. (no Refs)

29. DEACETYLATION OF 4-(5-ACETYLAMINO-2-FURYL)THIAZOLE TO 1-(4-THIAZOLYL)-3-CYANO-1-PROPANONE BY RAT LIVER TISSUES (MEETING ABSTRACT).

Swaminathan S, Bryan GT
Department of Human Oncology, University of Wisconsin Center for Health Sciences, Madison, WI, 53792
Proc Am Assoc Cancer Res; 23:334 1982

We postulate metabolic reduction of the rat carcinogen 4-(5-nitro-2-furyl)thiazole (NFT) to 1-(4-thiazolyl)-3-cyano-1-propanone (TCP). This may proceed from the nitro to the amino analog through the nitroso and N-hydroxylamino intermediates. Formation of TCP could occur at the stages of either N-hydroxylamino or amino intermediates by furan ring cleavage. To examine if 4-(5-amino-2-furyl)thiazole is a precursor for TCP, a stable model compound, 4-(5-acetylamino-2-furyl)thiazole (AAFT), was synthesized and its chemical identity established by spectroscopic and mass spectral analysis. Incubation with rat liver 10,000 g supernatant preparations resulted in the biotransformation of AAFT as evidenced by a decrease in absorption at 290 nm. Incubation of 14C-labeled AAFT followed by extraction with chloroform:ether (1:1) resulted in the recovery of a major portion (56%) of the radioactivity in the organic phase when the label was at the 2-position of the thiazole ring, while the major amount (82%) of radioactivity was recovered in the aqueous phase when the 1-14C-acetyl group was labeled. The radioactivity from the aqueous phase was extractable into the organic phase following acidification to pH 1, an observation consistent with deacetylation. Furthermore, the deacetylation product exhibited a mass spectrum, and retention times in gas and high pressure liquid chromatography, similar to that of synthetic TCP. (no Refs)

30. MORPHOLOGICAL AND NEOPLASTIC TRANSFORMATION OF SYRIAN HAMSTER EMBRYO FIBROBLASTS BY DIETHYLSTILBESTROL AND ITS ANALOGS.

McLachlan JA, Wong A, Degen GH, Barrett JC
Transplacental Toxicology Section, Natl. Inst. Environmental Health Sciences, NIH, Research Triangle Park, NC, 27709
Cancer Res; 42(8):3040-3045 1982

A mammalian cell culture system using normal, diploid Syrian hamster embryo fibroblasts was used as a model to study the ability of diethylstilbestrol (DES) and related compounds to induce neoplastic transformation. Like benzo(a)pyrene, a known chemical carcinogen, DES (0.01 to

10 ug/ml) induces morphological transformation of Syrian hamster embryo fibroblasts in vitro; the transformed colonies were indistinguishable from colonies of benzo(a)pyrene-transformed cells. The morphologically transformed colonies derived from either benzo(a)pyrene- or DES-treated cells were tumorigenic when injected into newborn hamsters. At doses of 0.01 to 1 ug/ml for 48 hr, DES did not inhibit or stimulate cell proliferation. Structural analogous of DES were also tested in the Syrian hamster embryo transformation system. Like DES; tetrafluoro-diethylstilbestrol, dimethylstilbestrol, and cis,cis-dienestrolmorphologically transformed Syrian hamster embryo cells. The transformation frequency of dimethylstilbestrol was much less than that of DES, tetrafluorodiethylstilbestrol, or cis,cis-dienestrol. Hexestrol, dimethoxydiethylstilbestrol, and trans,trans-dienestrol did not transform these cells. No correlation could be demonstrated between reported estrogenic potency of the compounds and their cell-transforming capacity. Structure-activity relationships developed for these chemicals suggest that metabolism via specific pathways plays a role in DES-induced cell transformation. (Author abstract) (33 Refs)

MODIFICATION OF CARCINOGEN METABOLISM

31. EFFECT OF BUTYLATED HYDROXYANISOLE (BHA) ON DOSE-RESPONSE FOR BENZO(A)PYRENE (BP) METABOLITE-DNA ADDUCTS IN MICE (MEETING ABSTRACT).

Anderson MW, White CM, Adriaenssens PI

National Institute of Environmental Health Science, Research Triangle Park, NC, 27709

Proc Am Assoc Cancer Res; 23:355 1982

The phenolic antioxidant, BHA, has been shown to be a potent inhibitor of the neoplastic effects of BP in mouse lung and forestomach. We previously showed that BHA treatment of mice inhibited BP metabolite-DNA adduct formation in the lung to the same degree that BP-induced pulmonary adenoma formation was inhibited. In this study the formation of BP metabolite-DNA adducts in lung, liver, and forestomach of control and BHA-treated female A/HeJ mice was examined as a function of BP dose (po) ranging from 2 to 1350 umol/kg. The major identified adduct in each tissue at each dose was the 7beta,8alpha-dihydroxy-9alpha,10alpha-epoxy-7,8,9,10 tetrahydro-BP (BPDEI)-deoxyguanosine adduct. The 7beta,8alpha-dihydroxy-9beta, 10beta-epoxy-7,8,9,10-tetrahydro-BP (BPDEII)-deoxyguanosine adduct and a BP-phenol-oxide-DNA adduct were also observed. In untreated animals the dose-response curves for these adducts were sigmoidal in each tissue. In forestomach the dose-response curve for BPDE-DNA adducts levels in BHA-treated mice was parallel to the curve for control animals and, thus, the inhibition (45%) of adduct formation was independent of BP dose. In contrast, BHA treatment diminished the curvilinear nature of the dose-response curves for BPDE adducts in lung and live. The dose-response curves in lung and liver of treated animals were approximately linear. The inhibition in lung (70%) and liver (80%) was highest at a BP dose of 0.3 mmol/kg. As BP dose approached zero, the inhibition of BPDE-DNA adduct formation decreased with BP dose and approached values of 40% (lung) and 55% (liver). (1 Ref)

32. EFFECT OF MONOOXYGENASE INDUCERS ON RAT MAMMARY PEROXIDASE AND ARYL HYDROCARBON HYDROXYLASE (AHH) (MEETING ABSTRACT).

Rogan E, Cavalieri E

Eppley Institute for Research in Cancer, Omaha, NE, 68105

Proc Am Assoc Cancer Res; 23:314 1982

Since horseradish peroxidase catalyzes binding of polycyclic aromatic hydrocarbons (PAH) by one-electron oxidation and peroxidase may activate PAH by the same mechanism, we studied the effect of monooxygenase inducers on rat mammary peroxidase, and compared it to induction of AHH. Female, 50-60-day-old Sprague-Dawley rats were treated for 2 days prior to killing with 5,6-benzoflavone (BF) or 3-methylcholanthrene (MC) by injection ip or sc at the second and fifth nipples on each side of the rat. BF and MC were injected ip in olive oil at 80 mg/kg and 40 mg/kg bw, respectively, and both sc at 50 nmole/nipple in 5 ul dimethyl sulfoxide (DMSO). Peroxidase and AHH were assayed with guaiacol and benzo[a]pyrene, respectively, as substrates. Peroxidase was significantly induced by ip injection of BF and possibly of MC, when compared to untreated controls. Olive oil caused a smaller, but significant, increase in peroxidase activity. The effect of BF and MC injected sc was less certain, because of the increased peroxidase activity caused by DMSO. Olive oil ip and DMSO sc significantly reduced AHH. However, BF injected ip overcame the solvent effect and significantly increased AHH, compared to the untreated and solvent groups. MC injected ip, and BF and MC injected sc reversed some of the decrease in AHH caused by olive oil and DMSO. The effects of monooxygenase inducers on peroxidase were greater than those on AHH. (no Refs)

33. SELENIUM ENHANCED CONJUGATION OF BENZO(A)PYRENE BY HEPATOCYTES (MEETING ABSTRACT).

Marshall MV, Gonzalez MA, Griffin AC

Southwest Foundation for Research and Education, San Antonio, TX, 78284

Proc Am Assoc Cancer Res; 23:278 1982

Previous studies have attributed anticarcinogenic properties to enhanced dietary intake of selenium. No mechanism of action has yet been determined, although several reports have demonstrated enhanced detoxification of chemical carcinogens requiring metabolic activation. The purpose of this study was to investigate the detoxification of benzo(a)pyrene (BaP) by hepatocytes isolated from rats fed a selenium supplementation of 4 ppm in their drinking water. Rats were fed a control diet or one containing 4 ppm Se (as Na2SeO(3)) for 15 days. After 11 days on the experimental diet, animals in both groups (control, Se) were injected with Aroclor 1254 to induce mixed function oxidase activity. Hepatocytes were isolated 4 days later and cultured with 50 uM 3H BaP for up to 2 h. In hepatocytes isolated from the Se group, an increase in sulfate, glucuronide, and glutathione conjugation was observed. An increase in dihydrodiol and phenol formation and a decrease in quinone formation was also observed for the free metabolites. In summary, dietary Se administration enhanced the conjugation of BaP. Increases in metabolism were also observed in the free metabolite fraction. The increase in dihydrodiol production also implicates an enhancement of epoxide hydrolase activity. The overall effect was to increase conversion of BaP to water soluble metabolites and conjugates. (no Refs)

34. THE INFLUENCE OF ASBESTOS ON THE FORMATION AND REMOVAL OF BENZO(A)PYRENE-DNA ADDUCTS IN A HAMSTER TRACHEAL EPITHELIAL CELL LINE (MEETING ABSTRACT).

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Proc Am Assoc Cancer Res; 23:236 1982

The effect of asbestos fibers (crocidolite and chrysotile) on the interaction of benzo(a)pyrene (BP) with a hamster tracheal epithelial cell line (HTE-B) has been investigated. When BP alone was incubated with HTE-B cells, 50% of the applied hydrocarbon was recovered as water soluble metabolites at 8 hr while 5% was recovered as intracellular unmetabolized BP. After 8 hr incubation with BP, the medium was replaced and a 50% reduction in alkylation was observed in 24 hr with about 80% removed by 5 days. High performance liquid chromatography separation of the DNA adducts demonstrated six adducts. Of these six adducts, two were rapidly removed while two were relatively poorly removed during the 5 day repair period. In comparative studies, BP was coated onto asbestos and applied to HTE-B cells. An enhanced uptake was observed with 80% BP associated with the cells after 1 hr. Metabolism was only slightly inhibited as compared to experiments without asbestos but at 8 hr nearly 50% of the applied hydrocarbon was retained by the cells in unmetabolized form. Analysis of repair was complicated by continued formation of alkylated products in DNA after removal of BP. However, after 24 hr post-treatment, only 5% of the applied BP remained in the cells. At 5 days, it appeared that removal of DNA-bound adducts was inhibited. Experiments with both crocidolite and chrysotile gave the same results. It is concluded that the cocarcinogenic effect of asbestos may be due to enhanced cellular uptake of BP as well as inhibition of subsequent DNA repair. (no Refs)

35. ENHANCED HEPATOTOXICITY OF AFLATOXIN B1 BY PRETREATMENT OF RATS WITH ETHANOL.

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Res Commun Chem Pathol Pharmacol; 36(3):477-491 1982

Hepatotoxicity of aflatoxin B1 (2.0 and 4.0 mg/kg ip) as determined by plasma enzyme activities (GPT and GOT), liver triglycerides and histopathologic changes was enhanced in rats pretreated with four oral doses of ethanol (4.0 g/kg each) at 48, 45, 24 and 21 hr prior to aflatoxin B1 administration. Pretreatment with ethanol (4.0 g/kg) slightly increased liver weight without changing hepatic microsomal protein contents. Also it caused an increase in microsomal aniline hydroxylase but a decrease in p-nitroanisole-o-demethylase, 48 hr after the first ethanol dose. In the rats pretreated with ethanol, aflatoxin B1 was metabolized at a higher extent to aflatoxins M1 and Q1. These results suggest that an increased hepatotoxicity of aflatoxin B1 after pretreatment with ethanol may presumably be due to an increase in microsomal formation of active aflatoxin B1 metabolite. (Author abstract) (36 Refs)

36. SELENIUM AND THE ACUTE EFFECTS OF THE CARCINOGENS, 2-ACETYLAMINOFLUORENE AND METHYLAZOXYMETHANOL ACETATE.

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Cancer Res: 42(8):2985-2989 1982

Selenium inhibits the development of 2-acetylaminofluorene-induced hepatic tumors and methylazoxymethanol-induced colon tumors. It has been suggested that selenium exerts these protective effects by inhibiting metabolic activation of the carcinogen. We have studied the effects of selenium upon the acute inhibition of RNA and DNA synthesis induced by 2-acetylaminofluorene or methylazoxymethanol in intact liver, regenerating liver, and colon of weanling male Sprague-Dawley rats. Some animals received selenium in the drinking water (4 ppm) for 1 wk, while others received a single injection of selenium (1 mg/kg ip) prior to being treated with the carcinogens. No protection against the effects of the carcinogens on RNA or DNA synthesis was noted with either treatment of selenium. Disulfiram did protect against the 2-acetylaminofluorene-induced inhibition of hepatic RNA synthesis, and pyrazole prevented the inhibition of RNA synthesis induced by methylazoxymethanol in both liver and colon. Serum selenium levels are reported. The data indicate that selenium does not influence the acute alterations induced by the carcinogens 2-acetylaminofluorene or methylazoxymethanol and suggest that the tumor-preventive effects of selenium are probably due to a mechanism other than interference with carcinogen activation and interaction with cellular macromolecules. (Author abstract) (34 Refs)

37. EARLY BIOCHEMICAL EVENTS COMPARING 2-ACETYLAMINOFLUORENE HEPATOCARCINOGENESIS AND 4-ACETAMIDOPHENOL HEPATOTOXICITY IN THE RAT (MEETING ABSTRACT).

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Proc Am Assoc Cancer Res; 23:209 1982

This study compares pyrimidine biosynthetic alterations of dihydroorotate dehydrogenase, uridine-5'-diphosphate kinase (UDP kinase), cytidine-5'triphosphate synthetase (CTP synthetase); and gamma-glutamyl transpeptidase in livers of rats fed 0.025% of the hepatocarcinogen 2-acetylaminofluorene (AAF) or 1.87% of the hepatotoxin, 4-acetamidophenol (AAP) in their diets. Results showed that within three days of AAF feeding dihydroorotate dehydrogenase specific activity was decreased to 0.6 of control while UDP kinase was increased 2.7-fold. After 14 days, a 2-fold increase in the activity of CTP synthetase was observed and by day 21 gamma-glutamyl transpeptidase specific activity was increased 8-fold. Histologically, acute centrilobular necrosis was observed in the livers of AAP fed animals. Yet no biochemical alterations resembling those induced by AAF were obtained. Dihydroorotate dehydrogenase specific activity was increased slightly as a result of hepatotoxicity but was decreased in hepatocarcinogenesis. UDP kinase and gamma-glutamyl transpeptidase specific activities were unaffected by AAP. CTP synthetase specific activity, elevated in hepatocarcinogenesis was decreased slightly in hepatotoxicity. (no Refs)

38. ESTRADIOL SUPPRESSES 2-AAF HEPATOCARCINOGENESIS IN MALE SPRAGUE DAWLEY RATS (MEETING ABSTRACT).

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Oklahoma Medical Research Foundation, Oklahoma City, OK, 73104
Proc Am Assoc Cancer Res; 23:919 1982

Twenty-two male Sprague Dawley rats (100 +/-8 gr) were fed a diet containing 0.05% 2-AAF for 16 weeks in an interrupted fashion (3 weeks with 2-AAF, one without). Each day eleven rats received (ip) 0.2 ml of stripped corn oil (CO) while the other eleven received 0.2 ml of oil containing 1 mg of suspended estradiol (ES). The animals, fed ad lib, gained weight over the next 120 days at an average of 0.5 gr/day/rat (ES) versus 1.8 gr/day/rat (CO). After 120 days, the ES treated rats had atrophied testes containing few cells while the CO rats testes appeared normal. At 90 and 120 days, hyperplastic nodules were very prominent in the CO rat livers and this was confirmed by histochemical staining of liver sections for gamma GT. The ES rats had neither gross appearing hyperplastic liver nodules, nor did gamma GT histochemistry indicate nodules. However, a few areas in the ES liver sections stained for gamma GT in a fashion reminiscent of remodeling areas. Microsomal styrene oxide hydrolase activity was induced to 147 +/-16 nmol/min/mg protein in CO livers. ES suppressed this induction to 31 +/-8 nmol/min/mg protein). Preliminary data on tumor incidence at 210 days showed two (of two) CO rats with pathologically certified carcinomas and two ES rats without tumors. The remainder of the rats will be scored for death due to hepatoma. ES may have a direct effect on male rat liver membrane enzyme regulation, since ES has been reported detected in male rat liver endoplasmic reticulum. (no Refs)

39. INHIBITION OF BIS(2-OXOPROPYL)NITROSAMINE-INDUCED COLON CARCINOGENESIS IN THE RAT DIETARY SELENIUM (MEETING ABSTRACT)

Birt DF, Runice CE, Julius AD, Salmasi S, Ryan W
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Proc Am Assoc Cancer Res; 23:349 1982

Dietary selenium (Se) was fed at levels of 0.1 and 2.0 ppm to MRC rats from 7 weeks of age until termination of the study at 58 weeks of age. Weekly injections of bis-(2-oxopropyl)nitrosamine (BOP) (5 mg/kg body weight, sc) began at 8 weeks of age and continued for the duration of the study. Body weights were not influenced by BOP treatment in either sex, or by Se treatment in males. However female body weights were decreased by feeding 2.0 ppm Se by comparison with 0.1 ppm Se for 50 weeks. Determinations of whole blood Se, and plasma and erythrocyte glutathione peroxidase activity (GSH-Px)- were made at 0, 10, 25 and 50 weeks after BOP treatment began. Blood Se rose with dietary Se at all intervals and plasma GSH-Px rose with dietary Se at 25 and 50 weeks, but neither measurement was influenced by carcinogen treatment. In addition erythrocyte GSH-Px increased with dietary Se at 50 weeks and was decreased after 25 weeks of BOP treatment at the low Se levels. The yield of colon adenocarcinomas was reduced in male rats from 32 in 26 rats in the 0.1 ppm Se group to 17 in 29 rats in the 2.0 ppm Se group. Adenocarcinoma incidences dropped from 50% to 28% in these groups. Colon adenocarcinomas were not induced in rats not treated with BOP or in female rats fed either selenium level and treated with BOP. (no Refs)

40. INDUCTION OF NITROSAMINE METABOLISM ENZYMES BY DIET AND CHEMICALS (MEETING ABSTRACT).

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Proc Am Assoc Cancer Res; 23:313 1982

The liver microsomal dimethylnitrosamine demethylase activity (DMNd) of rats was elevated 4-5 fold by the following treatments: (1) pyrazole injected ip at a dosage of 200 mg/kg body weight for 3-4 days, (2) ethanol present at 15-20% in drinking water for 7-10 days, 3) acetone or isopropanol administered po at a dosage of 2.5 ml/kg in a 25% solution for 1-2 days. The gross cytochrome P-450 content and NADPH-cytochrome c reductase activity were not significantly changed by these treatments. Fasting for 3 days caused a moderate increase in DMNd and a decrease in NADPH-cytochrome c reductase activity, but the DMNd was elevated by preincubating the microsomes with purified NADPH-cytochrome P-450 reductase. Thus, all the above treatments appeared to produce a similar type of alteration of microsomal enzymes. They all caused the appearance of new protein species with molecular weights around 52,000 dal. The induction of this protein was inhibited by treatment with COCl2 which also inhibited the induction of DMNd. The microsomes from the treated rats showed low Km values, ranging from 0.06-0.12 mM for different treatments, in the dimethylnitrosamine demethylase assay. NADPH-cytochrome P-450 reductase was shown to be an essential component enzyme of both the constitutive and induced DMNd. The results suggest that the above treatments induce specific cytochrome P-450 isozymes which are efficient in catalyzing the metabolism of nitrosamines. (no Refs)

41. RETINOIDS AS INHIBITORS OF ORTHO-AMINOAZOTOLUENE-INDUCED MUTAGENESIS IN THE SALMONELLA/LIVER MICROSOME TEST.

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Mutat Res; 104(4/5):225-231 1982

To determine the optimal conditions for ortho-aminoazotoluene (OAAT) mutagenicity in the Salmonella/liver microsome assay, three doses of OAAT (2, 4, and 8 ug/plate) were tested in the presence of various amounts of rat-liver homogenate (10, 20, 30, 50, 70, and 90 ul/plate). Thirty ul S9/plate yielded maximal mutagenicity, whereas the addition of larger or smaller amounts of rat-liver homogenate decreased mutagenic activity. OAAT was tested in the presence of various amounts of retinol, retinol acetate, and retinol palmitate ranging from 0-525 nanomoles/plate. Under optimal conditions (30 ul S9/plate), retinol inhibited the OAAT-induced mutagenicity almost completely. (10 Refs)

42. INFLUENCE OF METHIONINE ON THE MUTATION FREQUENCY IN SALMONELLA TYPHIMURIUM.

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Mutat Res; 94(2):331-338 1982

The ability to revert met- and his- markers was examined in a plate-system and the influence of methionine on mutation yields was noted. SB563 strain can be reverted to full prototrophy via stepwise isolation of his-met+ or the his+met- revertants. When the met marker was reversed first, reversibility of the his marker in the resulting SB563/met+ revertants decreased dramatically. This effect was due to the absence of methionine on the test plates; addition of methionine to the SB563/met+ revertants significantly enhanced reversion of the his marker. The observed effect of methionine reflects the necessity for intensive synthesis of some proteins in the bacterial cells with premutated lesions, or methionine acts on mutagenesis via the DNA methylation process. (16 Refs)

43. THE THIRD CLASS OF NEW TUMOR PROMOTERS, POLYACETATES (DEBROMOAPLYSIATOXIN AND APLYSIATOXIN), CAN DIFFERENTIATE BIOLOGICAL ACTIONS RELEVANT TO TUMOR PROMOTERS.

Fujiki H, Suganuma M, Nakayasu M, Hoshino H, Moore RE, Sugimura T

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Gan; 73(3):495-497 1982

Aplysiatoxin is a new class of potent tumor promoter and debromoaplysiatoxin may be a weak promoter. Aplysiatoxin and debromoaplysiatoxin showed the same potency on irritation of mouse ear and induction of ornithine decarboxylase activity on mouse skin, but debromoaplysiatoxin was much weaker than aplysiatoxin in induction of adhesion of HL-60 cells. (Author abstract) (12 Refs)

44. EFFECT OF ETHIONINE ON SAM METABOLISM AND DNA METHYLATION IN HYDRAZINE-TREATED RATS (MEETING ABSTRACT).

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Proc Am Assoc Cancer Res; 23:206 1982

Radioactive 7-methylguanine (7MG) and O6-methylguanine have been detected in liver DNA of rats treated with radioactive methionine and hepatotoxic doses of hydrazine. We have recently shown S-adenosylmethionine (SAM) to methylate DNA directly to produce these same derivative bases. In an attempt to determine if DNA methylation could be modulated by interfering with SAM metabolism, SAM levels, specific activity, and DNA methylation were monitored in hydrazine-treated rats also receiving ethionine. In rats treated with 500mg ethionine/kg 12 hours before administration of hydrazine (60mg/kg) and [3H]methionine (100uCi/hour, for 5 hours) no inhibition of 7MG formation was observed. SAM levels in these animals were slightly below normal, SAM specific activity was normal. Liver S-adenosylethionine concentrations at this time were 2umoles/g liver wet wt, normal SAM concentrations were 65nmoles/g liver wet wt. However, in rats treated with [3H]methionine (300uCi), ethionine (500mg/kg), and hydrazine (60mg/kg) at 15 min intervals, no 7MG was detected. In these rats liver SAM levels fell to 25% of normal within 15 min of ethionine administration. 7MG was detected in the DNA of rats receiving only [3H]-methionine and hydrazine. 5-Methylcytosine synthesis was not inhibited in rats treated with ethionine and hydrazine, and was increased in rats receiving ethionine 15 min before hydrazine. (no Refs)

45. EFFECT OF PYRIDOXAL DEFICIENCY ON PANCREATIC DNA DAMAGE AND NODULE INDUCTION BY AZASERINE (MEETING ABSTRACT).

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Proc Am Assoc Cancer Res; 23:264 1982

The purpose of this study was to determine whether the effects of azaserine on pancreas are pyridoxal-dependent. For DNA damage studies, weanling rats were fed a pyridoxal deficient diet containing 4-deoxypyridoxine, a pyridoxal antagonist, until deficiency was evident (10-12 days). They were then injected with azaserine 90 min before sacrifice. The deficient rats inhibited almost no pancreatic DNA damage (as determined by alkaline elution) in response to azaserine when compared to saline-treated rats on control diet. A structurally different pancreatic carcinogen, Ndelta-(N-methyl-N-nitrosocarbamoyl)-L-ornithine, caused DNA damage in both deficient and control groups. Distribution studies with 14C-azaserine showed that the absence of DNA damage was not due to the lack of azaserine transport into the pancreases of deficient animals. In another study, rats were treated with 4-deoxypyridoxine prior to a single azaserine treatment. Rats were killed 4 mo after azaserine administration. There was a significant reduction in the number of atypical acinar cell nodules in antagonist-treated animals compared to controls treated with azaserine but not with the antagonist. These results strongly indicate that azaserine metabolism and carcinogenicity are dependent on pyridoxal. (no Refs)

46. ISOLATION AND IDENTIFICATION OF KAHWEOL PALMITATE AND CAFESTOL PALMITATE AS ACTIVE CONSTITUENTS OF GREEN COFFEE BEANS THAT ENHANCE GLUTATHIONE (GSH) S-TRANSFERASE ACTIVITY (MEETING ABSTRACT).

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Proc Am Assoc Cancer Res; 23:346 1982

GSH S-transferase is a major detoxification system that catalyzes the binding of a variety of electrophiles, including reactive forms of carcinogens to GSH. Green coffee beans fed in the diet enhance the activity of this enzyme system in the mucosa of the small bowel and the liver of female ICR/Ha mice. Two compounds that produce a marked increase in GSH S-transferase activity were isolated from green coffee beans and identified. They are kahweol palmitate and cafestol palmitate. Both are diterpene esters. Twenty-four hours after 4 daily doses of these two compounds at 5 mg/mouse, GSH S-transferase activity is increased as follows test/controls: kahweol palmitate - liver 3.5, small bowel 5.6; cafestol palmitate - liver 3.0, small bowel 3.9. The free alcohols, ie kahweol and cafestol, and their monoacetates likewise increase GSH S-transferase activity. Palmitic acid does not. In the isolation, the diterpene esters were extracted from green coffee beans into petroleum ether. The petroleum ether extract was fractionated by preparative normal phase, and reverse phase liquid chromatography successively. Final purification with silver nitrate impregnated thin layer chromatography yielded the pure palmitates of cafestol and kahweol. The structures were determined by examination of the spectroscopic data of the esters and their parent alcohols, and by derivative comparison. Several compounds potent in increasing GSH S-transferase activity inhibit carcinogen-induced neoplasia. (no Refs)

47. INHIBITION OF CARCINOGENESIS OF THE RAT MAMMARY GLAND AND MOUSE URINARY BLADDER BY A RETINOID AND AN INDUCER OF INTERFERON SYNTHESIS (MEETING ABSTRACT).

McCormick DL, Becci PJ, Moon RC
Illinois Institute of Technology Research Institute, Chicago, IL 60616
Proc Am Assoc Cancer Res; 23:354 1982

Retinoids are potent inhibitors of chemical carcinogenesis of the mammary gland and urinary bladder in experimental animals. MVE-2 is a divinyl ether-maleic anhydride copolymer which induces interferon synthesis. These studies were conducted to determine the influence on chemical carcinogenesis of combined administration of MVE-2 and the retinoid N-(4-hydroxyphenyl)retinamide (4-HPR). In the mammary study, virgin female Sprague-Dawley rats received a single iv dose of 20 mg N-methyl-N-nitrosourea per kg body weight. In the bladder study, male C57BL/6 x DBA-2 F1 mice received 8 weekly ig doses of 7.5 mg (4-(butylnitrosoamino)-1-butanol). One week after the final carcinogen treatment, animals in both studies were randomized into groups of 50 as follows: (1) placebo diet (2) 4-HPR, 391 mg/kg diet (3) MVE-2, 25 mg/kg body weight, administered ip in 4 week cycles (3 weeks treatment, 1 week rest) throughout the study (4) MVE-2, 12.5 mg/kg, given as above (5) 4-HPR diet +— 25 mg MVE-2/kg (6) 4-HPR diet + 12.5 mg MVE-2/kg. In both studies, 4 HPR (group 2) and the high dose MVE-2 (group 3) treatments resulted in a significant inhibition of carcinogenesis. The low dose of MVE-2 (group 4) was not active in chemoprevention. No synergistic or additive interaction was observed between 4-HPR and MVE-2 at either dose level. These data suggest that either 4-HPR and MVE-2 inhibit carcinogenesis by a common mechanism, or, more likely, that the compounds have an antagonistic activity which precludes an additive or synergistic interaction in cancer inhibition. (no Refs)

MUTAGENICITY OF ACTIVATED METABOLITES OF CARCINOGENS

48. L5178Y TK +/- MOUSE LYMPHOMA CELL MUTAGENESIS ASSAYS OF 40 CODED COMPOUNDS (MEETING ABSTRACT).

Rudd CJ, Mitchell AD, Myhr BC, Caspary WJ, Poulton S, Lee YJ
SRI International, Menlo Park, CA, 94025
In Vitro; 18(3,part2):299 1982

The L5178Y TK +/- mouse lymphoma mutagenesis assay system is being validated by two laboratories using a common protocol to test coded compounds. Results have been obtained for 40 compounds representing members of 24 chemical classes. The results include the toxicity and mutagenicity of the compounds tested in both the presence and absence of a rat liver metabolic activation system. Experiments which met criteria for acceptable limits of toxicity and spontaneous mutation frequencies were used to evaluate each chemical's mutagenic response, and 98% agreement has been obtained between the laboratories. These results are compared with the results of testing the same compounds in other laboratories by other in vitro and in vivo approaches for the National Toxicology Program. Thus far, only four compounds, benz(a)anthracene, benzo(a)pyrene, calcium chromate, and 4-nitroquinoline-N-oxide, were positive in each type of assay; none was consistently negative. (no Refs)

49. USE OF AMES TEST TO DETERMINE PROCARCINOGEN ACTIVATION POTENTIAL OF A CELL LINE USED FOR MUTAGEN/CARCINOGEN TESTING (MEETING ABSTRACT).

Swierenga SH, Matula T
Drug Toxicology Division, Health and Welfare Canada, Ottawa K1A 0L2, Canada
In Vitro; 18(3,part2):288 1982

The successful use of mammalian cultured cells in mutagen/carcinogen testing depends on the presence (endogenous or exogenous) of adequate activation systems for procarcinogen metabolism. To determine whether an established cell line derived from rat liver (T51B) has retained the ability to activate a variety of procarcinogens after numerous passages in vitro, these compounds were tested with standard Ames Test, by substituting the tissue culture cells for the usual S-9 microsomes. Tester strains TA100, TA1538 and TA98 were preincubated with carcinogen, NADPH2 generating system, and aliquots of T51B cells for 1 h before plating for bacterial mutation. Quantitation of mutants formed after 48 h incubation showed that the liver cells had only a very weak capability of mediating bacterial mutation with benzo(a)pyrene, 3-methylcholanthrene, aflatoxin B2, and 2-acetylaminofluorene; but were potent activators of the aromatic amine 2-aminoanthracine, eliciting a dose reponse and a mutagenic effect comparable to standard S-9. Thus different cell lines may be 'specialists' for the activation of specific types of compounds and the use of exogenous activation systems is recommended. (no Refs)

50. MUTAGENICITY AND SYNTHESIS OF ALPHA-SUBSTITUTED N-NITROSAMINES: DERIVATIVES WITH DITHIOCARBAMIC ACID.

Pool BL, Bertram B, Wiessler M
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Carcinogenesis; 3(5):563-567 1982

Disulfiram (DSF) can considerably alter the organotropy of chemical carcinogens. For N-nitrosodimethylamine and for N-nitrosodiethylamine the organotropy is shifted from the liver to the nasal cavity or the esophagus, respectively. Whereas the influence of DSF or its metabolites on enzyme systems has been studied, little is known about its interaction with the carcinogens at a molecular level. Therefore, postulated reaction products of a series of alpha hydroxylated N-nitroso-dialkylamines and dithiocarbamate were synthesized and tested for mutagenicity in Salmonella typhimurium TA 1535. The results show that the compounds conjugated at a primary alpha-C-atom are not mutagenic, whereas those conjugated at a secondary alpha-C-atom are active. The primary N-nitroso-dithiocarbamates represent unique examples of inactivated dialkyl-nitrosamine derivatives. In addition, their formation in vitro was indirectly demonstrated. The possible role these inactivated compounds may play during the DSF-modulation of carcinogenesis will be discussed. (Author abstract) (16 Refs)

51. MUTAGENICITY OF THE OPTICAL ISOMERS OF THE DIASTEREOMERIC BAY-REGION CHRYSENE 1,2-DIOL-3,4-EPOXIDES IN BACTERIAL AND MAMMALIAN CELLS.

Wood AW, Chang RL, Levin W, Yagi H, Tada M, Vyas KP, Jerina DM, Conney AH

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Cancer Res; 42(8):2972-2976 1982

The mutagenic activities of the four optically pure (+)- and (-)-enantiomers of the two diastereomeric bay-region chrysene 1,2-diol-3,4-epoxides were evaluated in histidine-dependent strains of Salmonella typhimurium and in cultured Chinese hamster V79 cells. In strain TA98 of S typhimurium, (-)-1alpha,2 beta-dihydroxy-3beta,4beta-epoxy-1,2,3,4 tetrahydrochrysene was 5 to 10x more active than the other three optical isomers. However, in strain TA100 of S typhimurium and in Chinese hamster V79 cells, (+)-1beta,2alpha-dihydroxy-3alpha,4alpha-epoxy-1,2,3,4 tetrahydrochrysene was the most mutagenic diol-epoxide and was from 5 to 40x more active than the other three optical isomers. The bay-region (+)- and (-)-3,4-epoxy-1,2,3,4-tetrahydrochrysene isomers had identical mutagenic activities in all three systems. These studies indicate that the presence and orientation of the hydroxyl groups play an important role in modulating the mutagenic activity of bay-region epoxides of chrysene in both bacterial and mammalian cells. (Author abstract) (31 Refs)

52. MUTAGENICITY OF NITROAROMATIC HYDROCARBONS IN THE SALMONELLA ASSAY: STRUCTURE ACTIVITY RELATIONSHIPS (MEETING ABSTRACT).

Rao TK, Allen BE, Cox JT, Epler JL

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Fifth CIIT Conference on Toxicology: Toxicity of Nitroaromatic Compounds, January 28-29, 1982, Raleigh, North Carolina. Chemical Industry Institute of Toxicology 16 pp., 1982.

A selected group of nitroaromatic hydrocarbons was assayed for mutagenicity in the Salmonella histidine reversion assay and several useful conclusions were drawn, based on their chemical structure. Almost all the compounds were direct acting, in that they did not require any addition of exogenous metabolic enzymes (S-9 mix). Strains capable of detecting frameshift mutations (TA98 and TA100) were reverted by these compounds. A dependence on the carbon ring size was noted for mutagenic activity. The larger fused ring structures such as nitroperylene (5-ring) and nitropyrene (4-ring) were more mutagenic than nitronaphthalene (2-ring). Compounds with only one all-carbon ring (nitrobenzene, nitrotoluenes, nitroxylenes) were not mutagenic. However, ring substitution with nitrogen as in nitropyridine, nitrobenzimidazole and nitroquinoline resulted in significant mutagenic activities. Results obtained under aerobic and anaerobic conditions will be compared. The data presented would contribute to a growing information base on chemical structure/mutagenic activity relationships which can lead to a clearer understanding of the mechanism for biological activity. (no Refs)

53. MAMMALIAN ACTIVATION AND METABOLISM OF 1-NITROPYRENE (MEETING ABSTRACT).

Ball LM, Kohan MJ, Claxton L, Lewtas J
Health Effects Research Laboratory, U.S. EPA, Research Triangle Park, NC, 27711
Fifth CIIT Conference on Toxicology: Toxicity of Nitroaromatic Compounds, January 28-29, 1982, Raleigh, North Carolina. Chemical Industry Institute of Toxicology 16 pp., 1982.

We have used 1-nitropyrene (NP) as a model nitrated polycyclic organic compound (NPOC), to investigate potential genotoxicity in mammalian systems. NP was generally non-mutagenic in bioassays conducted in Chinese hamster ovary cells, and in the mouse lymphoma L5178Y system. However with the addition of a metabolic activation system consisting of the S-9 fraction from Arochlor-induced rat liver, NP proved to be more mutagenic than benzo(a)pyrene in the latter assay. NP also induced unscheduled DNA synthesis in primary rat hepatocytes. The ability of S-9 to activate NP was confirmed by assay in the Salmonella nitro-reductase-deficient strain TA98FR1, in which NP exhibits minimal 'direct-acting' mutagenicity. S-9 increased the mutagenicity of NP seven-fold,and microsomes derived from the S-9 produced a twenty-fold increase. 1-Aminopyrene and N-acetylaminopyrene, the principal reductive metbolic products of NP, have been identified by HPLC (high performance liqiud chromatography) in incubations of NP with S-9. Other metabolites were tentatively identified as phenols produced by aromatic ring oxidation. Thus some mammalian enzyme systems are indeed capable of carrying out the metabolic reactions associated with genotoxic activity in microbes. The contribution of the oxidative metabolic products to the geno- and cytotoxicity seen in mammalian cells remains to be evaluated more closely. (no Refs)

54. THE COOPERATIVE ROLE OF BACTERIAL AND MAMMALIAN ENZYMES IN MUTAGENIC ACTIVATION OF NITRO-PAH COMPOUNDS (MEETING ABSTRACT).

Pederson TC, Siak JS
Biomedical Science Department, GM Research Laboratories, Warren, MI, 48090
Fifth CIIT Conference on Toxicology: Toxicity of Nitroaromatic Compounds, January 28-29, 1982, Raleigh, North Carolina. Chemical Industry Institute of Toxicology 16 pp., 1982.

The NADPH-Dependent enzyme activity in rat liver microsomes can significantly increase the mutagenicity of several nitro-substituted PAH (polynuclear aromatic hydrocarbon) compounds in the Salmonella/S9 mutation assay under appropriated assay conditions. The enhanced mutagenicity of 2-nitrofluorene (2NF), 1-nitropyrene (1NP), 6-nitrochrysene (6NC) and 6-nitrobenzo(a)-pyrene (6NBaP) in the presence of S9 enzymes can be detected using strain TA98 or the niridazole-resistant strain TA98NR. The S9-dependent activation of 6NBaP, like that of BaP, can also be observed using the dinitropyrene-resistant strains TA98/1,8-DNP6 and TA98NR/1,8-DNP2. In contrast, there is little or no detectable activation of 2NF, 1NP or 6NC by S9 enzymes in assays employing the dinitropyrene-resistant strains, suggesting that the S9-dependent mutagenicity of these compounds towards TA98 and TA98NR requires bacterial nitroreductase activity for formation of the ultimate mutagenic metabolites. This interpretation is supported by experiments with 1NP which demonstrate that an extractable mutagenic metabolite accumulates during incubation with S9 enzymes. The chromatographic and spectroscopic properties of this metabolite suggest it is a hydroxylated derivative of 1NP. It exhibits a high mutagenicity with TA98 and TA98NR but is markedly less active towards the dinitropyrene-resistant strains. There is no evidence to suggest that the S9-dependent activation of 6NBaP involves bacterial nitroreductase activity. This compound may be activated entirely by S9 enzyme activity to form a reactive product such as an epoxide. Thus, the increased mutagenicity of a nitro-PAH compound in the Salmonella/S9 assay may be either dependent or independent of bacterial nitroreductase activities. (no Refs)

55. MUTAGEN FORMATION AFTER THE ADDITION OF NITRITE TO NORMAL HUMAN GASTRIC JUICE.

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Carcinogenesis; 3(5):597-598 1982

The World Health Organization (WHO) has recently recommended the use of a simple in vitro test (Nitrosation Assay Procedure, NAP) to allow the ranking of orally administered drugs. It was suggested that the ranking of drugs should be carried out on a reactivity scale, according to their ability to nitrosate in the presence of high concentrations of nitrite at low pH (3-4). The present study was undertaken to investigate the effect of adding the concentration of nitrite recommended for the NAP test (40 mM) to normal fasting human gastric juice. The data clearly demonstrate that such treatment results in the formation of derivatives with specific mutagenic activity for the bacterium Salmonella typhimurium TA1537. This strain was recommended for use in the NAP Test. Although the NAP test may be valid for its original purpose, in the absence of more physiologically relevant data it is invalid for use as a final arbiter in risk-benefit assessments. The possible formation of mutagenic species as a result of the nitrosation of natural gastric secretions should be considered when any risk-benefit assessment is made. (Author abstract) (18 Refs)

56. MUTAGENS PRODUCED BY THE PYROLYSIS OF OPIUM AND ITS ALKALOIDS AS POSSIBLE RISK FACTORS IN CANCER OF THE BLADDER AND OESOPHAGUS.

Malaveille C, Friesen M, Camus AM, Garren L, Hautefeuille A, Bereziat JC, Ghadirian P, Day NE, Bartsch H

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Carcinogenesis; 3(5):577-585 1982

Samples of opium pipe scrapings (opium dross, called sukhteh locally), but not of crude opium, collected in an area with a high incidence of esophageal cancer in north-east Iran, were shown to contain pro-mutagens, producing mostly frameshift mutations in Salmonella typhimurium strains TA1538 and TA98 after metabolic activation. Pyrolysis of opium and of its major alkaloid, morphine, yielded smoke condensates with mutagenic activities 10 and 100x higher, respectively, than that of the sukhteh samples tested. Heterocyclic aromatic hydrocarbons and primary aromatic amines present at different concentrations in these three pyrolysates are considered to be the major active principles. Opium addiction has been implicated as a risk factor in bladder cancer in humans and the ingestion of opium pyrolysates, in conjunction with dietary deficiencies, may be related to the high incidence of esophageal cancer in north-east Iran, although causality has not been established. (Author abstract) (29 Refs)

57. MUTAGENS IN LARGER FUNGI. I. FORTY-EIGHT SPECIES SCREENED FOR MUTAGENIC ACTIVITY IN THE SALMONELLA/MICROSOME ASSAY.

Sterner O, Bergman R, Kesler E, Magnusson G, Nilsson L, Wickberg B, Zimerson E, Zetterberg G

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Mutat Res; 101(4):269-281 1982

Forty-eight species of large fungi (mushrooms) were tested for chemical mutagens using the Ames Salmonella mutagenicity test with strains TA98, TA2637, and TA100; results for the crude mushroom extracts and six pure metabolites reportedly found in mushrooms are presented. Activity with S9 mix was between 0-50%, and in no case was the activity enhanced in the presence of microsomal enzymes. Significant mutagenic activity was found with isovelleral from Lactarius species, agaritine from Agaricus bisporus and related species, and beta-nitraminoalanine from Agaricus silvaticus. (21 Refs)

58. MUTAGENIC RESPONSES OF FIVE INDEPENDENT GENETIC LOCI IN CHO CELLS TO A VARIETY OF MUTAGENS. DEVELOPMENT AND CHARACTERISTICS OF A MUTAGEN SCREENING SYSTEM BASED ON SELECTION FOR MULTIPLE DRUG-RESISTANT MARKERS.

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Mutat Res; 94(2):449-466 1982

Response of several well characterized genetic markers such as those involving resistance to thioguanine, emetine, ouabain, 5-6-dichlororibofuranosylbenzimidazole, and methylglyoxal bisguanylhydrazone towards a number of direct- and indirect-acting mutagens was assessed in proline-requiring Chinese hamster ovary (CHO) cell line. Direct-acting alkylating and DNA-adduct forming agents such as beta-propiolactone, ethyleneimine, N-nitrosomethylurea, 4-nitroquinoline-N-oxide, methyl methanesulfonate, and ethyl methanesulfonate; DNA intercalating and cross-linking agents such as ICR-170, acridine orange, ethidium bromide, mitomycin C, and actinomycin D; and chemicals requiring microsomal activation in other systems such as benzo[a]pyrene, 7,12-dimethylbenz[a]anthracene, benzidine, and beta-naphthylamine were examined. The response of various agents was determined at only two or three concentrations which should have resulted in between 10-80% cell killing. Mutation frequencies of different genetic markers which were observed in the control and mutagen-treated cultures, as well as the mutagenesis significance ratio of various markers, which provide a measure of their relative mutagenic response are shown. Of the genetic loci, no one single locus showed higher response to all of the chemicals, instead, depending upon the chemical, specific loci were found to be more responsive than others. Results indicated that CHO cells possess significant capacity for the metabolic activation of many procarcinogens, and also underscore the merits of measuring the mutagenic response at multiple genetic loci in mutagen screening studies. (40 Refs)

BINDING OF CARCINOGENS AND THEIR METABOLITES TO MACROMOLECULES

59. EFFECTS OF BENZO[A]PYRENE DIOL EPOXIDE ADDUCTS ON DNA SYNTHESIS IN MAMMALIAN CELLS.

Rinaldy A, Lockhart ML, Deutsch JF, Ungers GE, Rosenberg BH
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Mutat Res; 94(2):383-391 1982

Effects of benzo[a]pyrene diol epoxide (BPDE) adducts in DNA were studied in CV1-P cells infected with SV40 virus treated with BPDE in vitro prior to infection. Replication in CV-1 monkey kidney cells of SV40 DNA containing an av of 11 anti-BPDE adducts/molecule were compared to that of similar DNA containing no adducts. The decreased replication of DNA from BPDE-treated virus may have resulted directly from the presence of BPDE adducts in the DNA, or it may have been due to a decrease in cellular uptake or uncoating of the virus, possibly caused by the presence of BPDE adducts in the viral capsid proteins. Although replication of the DNA of the BPDE-treated virus was initially low, in the course of time the ratio of treated tsA to deletion molecules approached that of the mock-treated control. Viruses with 11 adducts/DNA molecule were only approx 12% viable in spite of the fact that most or all of the DNA molecules are ultimately able to replicate. The loss of viability thus suggested either a persistent defect in transcription of the infecting DNA, caused by BPDE adducts that do not prevent replication and/or a high probability of producing defective progeny molecules during repair or bypass replication of parental molecules containing BPDE adducts. The 12% viability indicated an av of approx 2/11 lethal hits. Data for three adducts/molecule indicated that approx 7% of the adducts were lethal. Results implied that a minor adduct might be responsible for the the loss of viability. (19 Refs)

60. RELATIONSHIP BETWEEN EXCISION REPAIR AND THE CYTOTOXIC AND MUTAGENIC EFFECT OF THE 'ANTI' 7,8-DIOL-9,10-EPOXIDE OF BENZO[A]PYRENE IN HUMAN CELLS.

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Mutat Res; 94(2):435-447 1982

Effects of the anti isomer of 7,8-diol-9,10-epoxide of benzo[a]pyrene (anti BPDE) were studied in xeroderma pigmentosum XP12BE and normally excising diploid human cells (NF). To determine if the time available for excision repair prior to onset of semi-conservative DNA replication plays a significant role in decreasing the potentially mutagenic effect of anti BPDE, NF cells were synchronized by density inhibition, released, and treated at expression densities from a common stock soln of tritiated anti BPDE approx 16 or 1 hr prior to onset of S. The NF cells treated in situ just prior to S exhibited the highest frequency of induced mutations. The frequencies observed in NF cells treated in situ in early G1 approx 16 hr prior to S or treated in density-inhibited G0 state were significantly (12-to 16-fold) lower than those of NF cells treated just prior to S. No such difference was observed in the excision repair-deficient XP12BE cells. Results supported the hypothesis that the number of DNA lesions remaining unexcised during S determines the mutagenic effect of the agent. Results indicated that DNA replication occurred on templates containing unexcised residues and that the number of anti BPDE adducts remaining unexcised was approx the same in the replicated and the non-replicated fraction of parental DNA. At the onset of S, the number remaining bound in NF cells was approx 2.5 residues/10(6) nucleotides. (14 Refs)

61. ORGANOTROPIC DIFFERENCES IN METABOLISM AND DNA BINDING OF 7,12-DIMETHYLBENZ(A)ANTHRACENE IN HUMAN FETAL CELLS (MEETING ABSTRACT).

Oravec CT, D'Ambrosio SM
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In Vitro; 18(3,part2):288 1982

DMBA (7,12-Dimethylbenz(a)anthracene) is a potent polycyclic aromatic hydrocarbon carcinogen, both transplacentally and in the adult, when activated to an electrophilic form. The rate of metabolism and DNA binding capacity of DMBA was compared in vitro in cells derived from human fetal brain, dermis, kidney, liver, intestine and lung. Intestinal cells metabolized approximately 30%, while the other cells tested (brain, liver, dermal, lung and kidney) metabolized 2.5-10% of the DMBA during a 48 h period. Using HPLC (high performance liquid chromatography), qualitative as well as quantitative differences in the metabolite profiles were observed in each cell culture. The level of DMBA binding to cellular DNA was of the order: intesine greater than lung greater than liver greater than dermal greater than kidney. This order parallels the metabolic rate except that kidney was much lower than expected. These studies show that DNA binding and total metabolism is different in cells from different human fetal organs. (no Refs)

62. HORSERADISH PEROXIDASE/HYDROGEN PEROXIDE (HRP/H2O(2)) BINDING OF POLYCYCLIC AROMATIC HYDROCARBONS (PAH) BY ONE-ELECTRON OXIDATION (MEETING ABSTRACT).

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Proc Am Assoc Cancer Res; 23:239 1982

Several lines of evidence indicate that HRP/H2O2 catalyzes binding of PAH by one-electron oxidation. However, proof lies in elucidating adducts obtained between PAH and biologic macromolecules. The carcinogenic 6-methylbenzo[a]pyrene (BP-6-CH(3)), in which activation by one-electron oxidation occurs at the 6-methyl group, was accordingly used. Calf thymus DNA (1 mg/ml), HRP (Type II, 0.1 mg/ml), 5 X 10-4M H2O2 and 70 uM [14C]BP-6-CH3 were incubated in 0.067 M Sorenson buffer, pH 7, for 1 hr at 37 C. After purification DNA (1 mg/ml) in 0.05 M Bis-Tris, 5 mM MgCl2, pH 7.1 was incubated with 0.1 mg/ml deoxyribonuclease I for 3 hr at 37 C under argon. The mixture, partially saturated with (NH(4))2SO4, was extracted 3 times with n-butanol. The residue, after evaporation of n-butanol, was analyzed by reverse-phase high performance liquid chromatography and its profile was compared to that from the hydrolyzed BP-6-CH2BR and DNA. Only a major adduct was present in the HRP/H2O(2)-activated system and the same adduct was also in the BP-6-CH2BR-DNA system. Both collected adducts co-chromatographed in 3 additional elution systems with the adduct obtained from deoxyguanosine (dG) and BP-6-CH2Br. Nuclear magnetic resonance spectra of the synthetic adduct showed that BP-6-CH3 binds through the methyl group to the 2-amino group of dG. Thus, structure elucidation of the HRP-H2O(2)-catalyzed adduct between BP-6-CH3 radical cation is the reactive intermediate responsible for the binding and HRP/H2O2 activation occurs by one-electron oxidation. (1 Ref)

63. FORMATION OF A 7-HYDROXYMETHYL-12-METHYLBENZ[A]ANTHRACENE-DNA ADDUCT FROM DMBA IN MOUSE EPIDERMIS (MEETING ABSTRACT).

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Proc Am Assoc Cancer Res; 23:244 1982

The present study was designed to investigate the role of 7-hydroxymethyl-12-methylbenz[a]anthracene (7-OHM-12-MBA) in the covalent binding of DMBA (dimethylbenzanthracene) to mouse epidermal DNA. The covalent binding of [3H]7-OHM-12-MBA to mouse epidermal DNA was compared with [3H]DMBA. Twenty-four hours after application of [3H]7-OHM-12-MBA (400 nmol) or [3H]DMBA (10 nmol) to the skins of SENCAR mice, the covalent binding was 29.0 or 4.5 pmol/mg epidermal DNA, respectively. The isolated DNA samples were hydrolyzed to deoxyribonucleosides and chromatographed on Sephadex LH20 columns. With DMBA, four distinct DMBA-DNA adduct peaks eluted after the p-(nitrobenzyl)-pyridine (p-NBP) marker. A fifth, early eluting peak, cochromatographed with p-NBP marker. When [3H]7-OHM-12-MBA was applied to the skins of mice, three distinct DNA-adduct peaks were observed. The major 7-OHM-12-MBA-DNA adduct eluted with the p-NBP marker and cochromatographed on high performance liquid chromatography with the early eluting DMBA-DNA adduct. The other 7-OHM-12-MBA-DNA adducts did not cochromatograph with any DMBA-DNA adducts. Interestingly, benzo[e]pyrene, which markedly inhibited DMBA tumor-initiation and DNA-adduct formation in SENCAR mice, had no effect on DNA-adduct formation with 7-OHM-12-MBA. The results suggest that a hydroxymethyl-metabolite gives rise to a minor DMBA-DNA adduct in mouse skin and that 7-OHM-12-MBA, when applied topically, may be processed by epidermal cells in a manner different from that of DMBA. (2 Refs)

64. REVERSAL OF CYTOSOLIC INHIBITION OF NUCLEAR AND MICROSOMAL MEDIATED BINDING OF AFLATOXIN B1 (AFB1) TO DNA BY EPOXIDES (MEETING ABSTRACT).

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Department of Biochemistry, Fels Research Institute, Temple University Medical School, Philadelphia, PA, 19140
Proc Am Assoc Cancer Res; 23:364 1982

Involvement of hepatic GSH S-transferases is indicated by cytosolic inhibition of nuclear and microsomal mediated binding of AFB1 to DNA. We have now examined effects of 1mM levels of trichloropropene oxide (TCPO) and styrene oxide (SO) on this inhibition process. Intact rat and hamster liver nuclei, microsomes and cytosols were used for these studies. Radioactivity present in DNA isolated by a modified Marmur procedure indicated AFB1 binding to DNA. With hamsters, 250 pmoles of [3H]AFB1 were bound to calf thymus DNA in the microsome mediated assay. Presence of either TCPO or SO did not have any stimulatory effect on this binding. Cytosol inhibited the microsome mediated AFB1-DNA binding by 70%. However, presence of either TCPO or SO reversed the cytosolic inhibition completely. In separate experiments, SO also inhibited the formation of AFB1-GSH conjugate. Intact nuclei formed 40-80 pmoles of [3H]AFB1 bound to endogenous DNA with or without microsomes. Presence of cytosol inhibited this binding by 80%. Addition of either epoxide reversed the cytosolic inhibition completely. These epoxides produced similar effects with rat liver fractions. These results provide additional evidence that GSH S-transferases are involved in cytosolic inhibition of nuclear and microsomal mediated AFB1 binding to either exogenous or endogenous DNA. (1 Ref)

65. N-2-ACETYLAMINOFLUORENE MODIFICATION OF POLY(DG-M5DC).POLY(DG-M5DC) INDUCES THE Z-DNA CONFORMATION.

Santella RM, Grunberger D, Nordheim A, Rich A
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Biochem Biophys Res Commun; 106(4):1226-1232 1982

Carcinogen induced conformational chages and the effect of N-2-acetylaminofluorene (N-Aco-AAF) modification on poly(dG-m5dC).poly(dG-m5dC) were investigated. The circular dichroism spectra of poly(dG-m5dC).poly(dG--m5dC) with various levels of acetylaminofluorene (AAF) modification are presented. With increasing levels of AAF, a decrease in the positive band at 280 nanometer (nm) and an increase in the negative band at 255 nm was observed. A sample with 3.5% modification underwent the B to Z transition with increasing Mg++ concentrations. A DNA sample modified with [14C] labeled AAF to an extent of 8.5% showed approx 50% digestion with S1 nuclease after 3 hr. In contrast, a 17.5% AAF modified sample of poly(dG-m5dC).poly(dG-m5dC) showed only 14% digestion after 3-hr incubation with S1 nuclease. The equilibrium binding level of the various polymers as a function of the concentration of N-Aco-AAF was determined. At the lowest concentration of N-Aco-AAF added, the methylated polymer was modified to a level of 6% compared to 3% with the unmethylated polymer. At higher concentrations of N-Aco-AAF, the level of AAF binding in the methylated polymer rose more rapidly than in the unmethylated polymer. Thus, the order of reactivity with AAF is poly(dG-m5dC).poly(dG-m5dC) greater than poly(dG-dC).poly(dG-dC) greater than poly(dG).poly(dC). Results indicated that the alternating polymer poly(dG-m5dC).poly(dG-m5dC) undergoes the B to Z transition at lower levels of AAF modification (10%) than required to convert the non methylated polymer (greater than 20%). (18 Refs)

66. DNA-METHYLATION BY NITROSOCIMETIDINE AND N-METHYL-N'-NITRO-N-NITROSOGUANIDINE IN THE INTACT RAT.

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Chem Biol Interact; 40(2):149-157 1982

The ability of the nitroso derivative of the drug cimetidine to interact with cellular macromolecules in the intact rat was investigated. Radio-labeled nitrosocimetidine was shown to methylate DNA in a variety of tissues in the rat after oral administration. Radioactivity was also detected in the RNA and protein extracted from these same tissues. Methylation of DNA by the parent compound, cimetidine, as not detected in any of the tissues studied. For comparison, the DNA methylation produced by the carcinogen N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) dosed orally was measured. DNA alkylation by MNNG was found to be approx 2-36x greater than that produced by NC, varying with the tissues studied. The highest yield of DNA alkylation was found in the stomach for MNNG and the small intestine for nitrosocimetidine suggesting pharmacokinetic differences. (Author abstract) (23 Refs)

67. CELL SPECIFICITY IN HEPATOCARCINOGENESIS: PREFERENTIAL ACCUMULATION OF O(6)-METHYLGUANINE IN TARGET CELL DNA DURING CONTINUOUS EXPOSURE OF RATS TO 1,2-DIMETHYLHYDRAZINE.

Bedell MA, Lewis JG, Billings K C, Swenberg JA
Dept. Pathology, Chemical Industry Inst. Toxicology, Research Triangle Park, NC, 27709
Cancer Res; 42(8):3079-3083 1982

Concentrations of the major methylated DNA purines were determined in two liver cell populations of Fischer 344 rats during administration of 30 ppm 1,2-dimethylhydrazine (SDMH) in the drinking water for periods of up to 4 wk. Quantitation of 7-methylguanine and O6-methylguanine (O6MG) was achieved by highly sensitive optical methods following separation of DNA bases by high-performance liquid chromatography. Overall alkylation as indicated by the concentration of 7-methylguanine was near max in both hepatocytes and liver nonparenchymal cells by the third day of SDMH administration. Similar amounts of 7-methylguanine were present in the two liver cell populations at seven of nine time points during 4 wk of exposure. In contrast, dramatic differences in the cumulative concentrations of O6MG were seen in the two cell populations. Nonparenchymal cells accumulated O6MG during the first 8 days of exposure and had up to a 30-fold greater concentration of this product than did the corresponding hepatocytes. In the hepatocytes, a rapid decline in O6MG concentration was observed between 1 and 3 days of exposure to SDMH. Thereafter, only low levels of this promutagenic lesion were present in hepatocytes. Exposure of rats to the same regimen of SDMH for up to 10 mo caused angiosarcomas in the livers of over 90% of the animals, while hepatocellular carcinomas occurred in only 40%. Thus, a strong correlation exists between the inability to repair O6MG and cell specificity for carcinogenesis. (Author abstract) (50 Refs)

68. N-METHYLOLPENTAMETHYLMELAMINE, AN ALKYLATING METABOLITE OF HEXAMETHYLMELAMINE (MEETING ABSTRACT).

Ames MM, Sanders ME, Tiede WS
Mayo Clinic, Rochester, MN, 55905
Proc Am Assoc Cancer Res; 23:3 1982

Hexamethylmelamine (HMM) is an investigational antitumor agent with activity against several types of human cancers. Metabolism has been implicated in the activity of HMM, but the mechanism of action of the drug is not known. We previously demonstrated that radiolabeled HMM is metabolized by hepatic microsomal monooxygenases to reactive intermediates which covalently bind to microsomal proteins. We have now shown that when calf thymus DNA is added to microsomal incubation mixtures, radiolabeled HMM is activated to intermediates which covalently bind to the DNA. Binding of radiolabeled HMM to DNA is NADPH and O2 dependent, inhibited by CO or SKF525A, and increased by microsomes from animals pretreated with phenobarbital. To evaluate the possibility that N-methylolpentamethylmelamine (MPMM), the intermediate in HMM demethylation, is an intermediate in the metabolic activation of HMM, we have synthesized [14C]-ring labeled MPMM. Incubation of radiolabeled MPMM (in the absence of cofactors required for metabolism) with microsomal protein and with calf thymus DNA results in covalent binding of radiolabel to protein and DNA. MPMM covalent binding to protein is maximal immediately after initiation of the incubation. Covalent binding to DNA is maximal at the end of the 60 minute incubation. This difference between the time course of MPMM binding to protein and DNA is similar to the difference in the time course of covalent binding to protein and DNA when HMM is incubated with microsomal preparations. Hydrolysis of precipitated and washed microsomal protein following incubation of HMM or MPMM yields only the demethylated metabolite of HMM (pentamethylmelamine) as expected if MPMM is the bound species. (1 Ref)

69. IDENTIFICATION OF CYSTEINE AND METHIONINE ADDUCTS FORMED BY REACTIONS WITH 2,2',5,5'-TETRACHLOROBIPHENYL-3,4-OXIDE (TCB-O) IN VITRO (MEETING ABSTRACT).

Preston BD, Miller JA, Miller EC
McArdle Laboratory for Cancer Research, University of Wisconsin, Madison, WI, 53706
Proc Am Assoc Cancer Res; 23:238 1982

TCB (2,2',5,5'-Tetrachlorobiphenyl), a major component of the hepatic tumor promoting agent Aroclor 1254, is metabolized in the rat via TCB-O. TCB undergoes metabolism-dependent binding to proteins and is converted to methylsulfide and methylsulfone derivatives in rodents. We have used uv, infra-red, 1H-nuclear magnetic resonance, and mass spectral techniques to characterize the products formed from reactions of TCB-O with L-cysteine and N-acetyl-L-methionine in vitro. Incubations of TCB-O with L-cysteine in ethanol:Tris buffer solution at pH 7.4, 37 C gave rise to 6% reaction of TCB-O in 25 hr to form a single product peak isolated by high pressure liquid chromatography. This peak was identified as a mixture of 3-and 4-(cysteine-S-yl)-TCB in about a 1:1 ratio. When TCB-O was reacted with L-cysteine in dimethyl sulfoxide:phosphate buffer solution (pH 7.4, 37 C), four additional product peaks were formed. Three of these minor products have been partially characterized as a (cystein-S-yl)-dihydro-hydroxy-TCB, a (TCBthio)-TCB, and a (TCBthio)-dihydro-hydroxy-TCB. Incubations of TCB-O with N-acetyl-L-methionine in ethanol:Tris buffer solution at pH 7.4, 37 C gave rise to 0.3% reaction of TCB-O in 48 hr to form equal amounts of 3-and 4-(methylthio)-TCB. Methylsulfonyl-TCBs were not detected in these reactions. These results suggest that TCB-O may be a metabolic intermediate of TCB responsible for protein binding and the formation of methylthio-TCB metabolites in vivo. (2 Refs)

70. EVIDENCE FOR MICROSOME-MEDIATED COVALENT BINDING OF DIETHYLSTILBESTROL TO DNA OR NUCLEOTIDES (MEETING ABSTRACT).

Liehr JG, DaGue BB
University of Texas Health Science Center, Houston, TX, 77025
Proc Am Assoc Cancer Res; 23:916 1982

In order to examine the possible role of estrogenic hormones as initiators of carcinogenesis, binding of the synthetic estrogen diethylstilbestrol (DES) to deoxynucleosides and calf thymus DNA was studied in an in vitro microsome-mediated reaction system. Binding levels were influenced by the reaction time, source of microsomes, and concentrations of DES, DNA, and microsomal cyt P450 (or P448) used in the reaction system. Reactions of 14C-DES (56 mCi/mmole) with 0.36 mM calf thymus DNA (heat denatured) or 3.3 mM dGMP catalyzed by phenobarbital-induced rat liver microsomes for 2.5 hrs produced 1300 and 50 adducts/ 10(6) nucleotides x nmole cyt P450), respectively. Binding of DES to DNA and dGMP in the presence of boiled microsomes was 1% and 10%, respectively, of that found in active microsome catalyzed reactions. Evidence for the covalent nature of DES binding to DNA and deoxynucleotides was obtained from the persistence of bound radioactivity after exhaustive extraction of reactions with organic solvents and, in the case of DNA, multiple precipitations from ethanol. Furthermore, it has been possible to separate by reverse phase high pressure liquid chromatography unreacted deoxynucleosides and the radioactive DES-deoxynucleosides obtained from organic solvent-extracted and alkaline phosphatase-treated binding reactions of 14C-DES and deoxynucleotides. (no Refs)

71. ALKYLATION OF GUANINE BY N-PROPYLDIAZONIUM ION. MOLECULARITY IS A FUNCTION OF BOTH NUCLEOPHILE AND ELECTROPHILE (MEETING ABSTRACT).

Scribner JD, Ford GP
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Proc Am Assoc Cancer Res; 23:236 1982

It has been reported that n-propyldiazonium ion alkylates N-7 of guanine in rat liver DNA to give 7-n-propylguanine, evidence that this ion reacts bimolecularly, without the formation of carbonium ions. It appeared to us, however, that N-7 of guanine may act as a highly nucleophilic trapping agent, and that weaker nucleophiles, such as O6, would react only with the less selective free carbonium ion. This was tested in vitro and in vivo, and theoretical studies undertaken to explain the results. Treatment of guanosine in water with n-propylnitrosourea gave a 3:1 ratio of O6/7 alkylation products. The only detectable O6 adduct was O(6)-isopropylguanosine, while the only detectable N-7 adduct was 7-n-propylguanosine. (3H)-Di-n-propylnitrosamine was injected into rats, which were sacrificed 12 hr later, and the liver DNA and RNA isolated. Portions of the RNA were digested enzymatically or with 1N HCl. The enzyme digest contained standard adducts, which were reisolated by ethyl acetate extraction and thin layer chromatography. After rechromatography of the standards, the specific activity of O(6)-i-propylguanosine was 7x higher than that of O(6)-n-propylguanosine. The acid digest was chromatographed directly with standards on a high resolution ion-exchange column, with a result like that of Park, et al. Thus we have shown that, while N-7 traps the n-propyldiazonium ion in a bimolecular reaction, O6 reacts predominantly in a manner which permits prior decomposition and rearrangement of the alkyl group, ie, alkylation of O6 has the properties of a unimolecular reaction. (1 Ref)

72. LABELED 1,N(6)-ETHENOADENOSINE AND 3,N(4)-ETHENOCYTIDINE IN HEPATIC RNA OF MICE GIVEN [ETHYL-1,2-3H OR ETHYL-1-14C] ETHYL CARBAMATE (URETHAN).

Ribovich ML, Miller JA, Miller EC, Timmins LG
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Carcinogenesis; 3(5):539-546 1982

Injection of a single dose of [ethyl-1,2-3H] or [ethyl-1-14C]ethyl carbamate into 12-day old male [C57BL/6 x C3H/He]F1 mice or of [ethyl-1,2-3H]ethyl carbamate into adult male A/Jax mice resulted in the formation of labeled 1,N6-ethenoadenosine and 3,N4-ethenocytidine adducts in the hepatic RNA. These adducts were characterized by comigration on HPLC of 3H or 14C in enzymatic hydrolysates of the RNA with synthetic standards. Both the ethenoadenosine and ethenocytidine were further characterized by their conversion to acetylated products that comigrated with acetylated synthetic standards. The ethenoadenosine was also converted by anhydrous trifluoroacetic acid to a product that comigrated with synthetic 1,N6-ethenoadenine. The levels of adducts in the hepatic RNA 12 hr after a single injection of 0.5-0.6 mg of ethyl carbamate/g body wt were 6-10 and 2-3 pmol/mg RNA of ethenoadenosine or ethenocytidine, respectively. No labeled ethenoadenosine or ethenocytidine could be detected in the hepatic RNA of mice given [1-14C]ethanol, an enzymatic hydrolysis product of ethyl carbamate. These data indicate that ethyl carbamate may be metabolically activated by dehydrogenation to vinyl carbamate and subsequent epoxidation of the latter compound as previously proposed. Vinyl carbamate epoxide may form etheno derivatives in a manner analogous to that demonstrated for chloroethylene oxide, an electrophilic metabolite of vinyl chloride. Vinyl carbamate has been shown to have the same spectrum of tumor induction as ethyl carbamate but to be much more active than the latter carcinogen. (Author abstract) (37 Refs)

73. FORMATION OF 6-DIMETHYLCARBAMYLOXY-DGUO, 6-DIMETHYLAMINO-DGUO AND 4-DIMETHYLAMINO-DTHD FOLLOWING IN VITRO REACTION OF DIMETHYLCARBAMYL CHLORIDE WITH CALF THYMUS DNA AND 6-DIETHYLCARBAMYLOXY-DGUO FOLLOWING IN VITRO REACTION OF DIETHYLCARBAMYL CHLORIDE WITH CALF THYMUS DNA.

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Chem Biol Interact; 40(2):209-231 1982

The rodent carcinogens dimethylcarbamyl chloride (DMCC) and diethylcarbamyl chloride (DECC) react with dGuo (pH 7.0-7.5, 37 C, 4 hr) to form the O6-acyl derivatives 6-dimethylcarbamyloxy-2'-deoxyguanosine (6-DMC-dGuo) and 6-diethylcarbamyloxy-2'-deoxyguanosine (6-DEC-dGuo), respectively. Reaction of DMCC with dThd under identical conditions yielded 4-dimethylamino-thymidine (4-DMA-dThd). Compounds 6-DMC-dGuo and 6-DEC-dGuo undergo a nucleophilic aromatic substitution reaction with dimethylamine (DMA) to form 6-dimethylamino-2'-deoxyguanosine (6-DMA-dGuo) via displacement of the C-6 dialkylcarbamyloxy moiety. The substitution reaction did not take place when diethylamine or NH3 were substituted for DMA. The structures of the new compounds 6-DMC-dGuo, 6-DEC-dGuo, 4-DMA-dThd and 6-DMA-dGuo were deduced from chemical analyses and syntheses, UV and nuclear magnetic resonance (NMR) spectra and electron impact, isobutane chemical ionization and source insertion isobutane chemical ionization mass spectra. It was postulated that 4-DMA-dThd was formed following reaction of the transient intermediate 4-DMC-dThd with DMA formed by hydrolysis of DMCC. Calf thymus DNA was reacted in vitro with DMCC (pH 7.0-7.5, 37 C, 4 hr) and the modified DNA hydrolyzed enzymatically to 2'-deoxynucleosides. Compounds 6-DMC-dGuo, 4-DMA-dThd and 6-DMA-dGuo were identified in the hydrolysate by high-pressure liquid chromatography (HPLC). In an identical manner 6-DEC-dGuo was identified following in vitro reaction of DECC with calf thymus DNA. Compounds 6-DEC-dGuo and 6-DMC-dGuo possess novel structures with respect to the types of adducts known to be formed between carcinogens and bases in DNA. The implications of these findings with respect to chemical mutagenesis and carcinogenesis is discussed. The structural relationship between N4-dimethyl-5-methylcytosine (4-dimethylamino-Thy) formed in DNA following in vitro reaction with DMCC and 5-methylcytosine, the only modified base found in vertebrate DNA is noted. (Author abstract) (41 Refs)

ALTERATION OF MIXED FUNCTION OXIDASES BY CARCINOGENS

74. EFFECTS OF DIETARY AND IN VITRO 2(3)-T-BUTYL-4-HYDROXYANISOLE AND OTHER PHENOLS ON HEPATIC ENZYME ACTIVITIES IN MICE.

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Br J Cancer; 45(6):935-944 1982

Six phenols [2(3)-t-butyl-4-hydroxyanisole (BHA), 2-t-butylphenol, 4-methoxyphenol, 4-methylmercaptophenol, t-butylhydroquinone and 2,6-di-t-butylphenol] previously shown to be inhibitors of benzo(a)pyrene-induced neoplasia, were examined for their ability to induce in vivo changes in hepatic mono-oxygenase and detoxication enzyme activities, and to act as monooxygenase inhibitors when added in vitro. (1) Generally it was found that cytochrome P450 levels were depressed, only 2,6-di-t-butylphenol caused a two-fold induction (2) Mono-oxygenase activities were significantly altered; BHA and 2,6-di-t-butylphenol caused microsomes to show substantial increases in aniline hydroxylase and peroxidase activities. These microsomes, along with 4-methoxyphenol microsomes, also showed a substantial reduction in DNA binding of benzo(a)pyrene (BaP) metabolites relative to metabolism. (3) Detoxication enzymes glutathione S-transferases and epoxide hydratase were readily induced, the order of effectiveness being: BHA approx = 2,6-di-t-butylphenol greater than 4-methoxyphenol greater than 2-t-butylphenol approx = 5-butylhydroquinone (4-methylmercaptophenol failed to induce). (4) In vitro ability to inhibit BaP metabolism and DNA-binding ability was: 2,6-di-t-butylphenol greater than or equal to BHA approx = 2-5-butylphenol greater than 5-butylhydroquinone greater than 4-methylmercaptophenol greater than 4-methoxyphenol. (5) Ability in vitro to discharge the activated oxygen complex of cytochrome P450 was: 2,6-di-t-butylphenol approx = 2-t-butylphenol greater than BHA greater than t-butylhydroquinone greater than 4-methylmercaptophenol greater than 4-methoxyphenol. The results are consistent with the theory that inhibition of neoplasia is related to inducibility of detoxication enzymes, though alterations in cytochrome P450 could play a significant role in some cases. (Author abstract) (39 Refs)

75. EFFECTS OF POSTNATAL PHENOBARBITAL EXPOSURE AND NUTRITIONAL STATUS ON THE MIXED-FUNCTION OXIDASE SYSTEM AND THE FORMATION OF AFLATOXIN MACROMOLECULAR ADDUCTS IN ADULT RATS.

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Diss Abstr Int [B]; 42(12,pt1):4747-B 1982

It was hypothesized that environmental conditions imposed on animals during sensitive periods of mixed-function oxidase (MFO) development during the perinatal period might permanently alter these carcinogen metabolizing enzymes and thus the biologic activity of carcinogen in adult animals. Two treatments, neonatal exposure to phenobarbital (PB) and maternal protein deprivation were employed as experimental models to study the impact of the postnatal environment on (1) the in vivo disposition of aflatoxin B1 (AFB1) and (2) hepatic MFO activities in adult offspring. PB and its metabolites were transmitted to F1 progeny in the milk via suckling whereas postnatal maternal protein deprivation restricted the quantity and perhaps the quality of milk available to suckling pups, and therefore altered the nutritional status of the neonate. It was observed that postnatal exposure to PB and the nutritional status of the preweanling animal permanently altered the ontogenetic expression of the MFO system in adult male rats. However, only early exposure to PB altered the metabolic activation of the hepatocarcinogen, AFB1, later in life. Moreover, this effect was apparently dose-dependent--that is, rats suckled by dams administered PB (40 mg/kg) demonstrated a 40% increase in AF-DNA adducts when AFB1 was administered at 9 months of age, but a PB dose of 60 mg/kg caused a subsequent 40% reduction in AF-DNA adduct formation in adult male rats. (no Refs)

76. THE TCDD RECEPTOR IN RAT INTESTINAL MUCOSA AND ITS POSSIBLE DIETARY LIGANDS.

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Nutr Cancer; 3(3):134-144 1982

Induction of aryl hydrocarbon hydroxylase (AHH) by polycyclic aromatic hydrocarbons and other inducers such as 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) is known to occur following binding of the inducer to a soluble receptor protein similar to steroid hormone receptors. This receptor is usually called the TCDD receptor, since TCDD has the highest affinity of all known ligands for the receptor. In the present paper, a receptor for TCDD in cytosol from rat intestinal mucosa has been studied, using isoelectric focusing in polyacrylamide gel. This receptor's biochemical properties were found to be similar to those of the TCDD-receptor in rat liver cytosol. The dissociation constant (Kd) of the 3H-TCDD-receptor complex in rat intestinal mucosa was 0.7-3.1 nM, and it was present at a concentration of 70-80 fmol/mg protein. Starvation did not significantly increase the receptor level. The affinities of some potential dietary ligands for the TCDD receptor in rat intestinal mucosa were also studied. Indole-3-carbinol had 1/2,600 of the affinity of TCDD for the receptor protein. Butylated hydroxyanisole (BHA), transstilbene oxide and quercetinpentamethylether competed even more weakly with 3H-TCDD for binding to the receptor. The biological significance of the occurrence of low-affinity ligands of dietary origin for the TCDD receptor is uncertain at the present time. (Author abstract) (37 Refs)

77. GENETIC DIFFERENCES IN THE INDUCTION OF ARYL HYDROCARBON HYDROXYLASE AND ITS COMPONENTS BY 3-METHYLCHOLANTHRENE IN LIVER AND LUNG MICROSOMES AMONG FOUR STRAINS OF GUINEA PIGS.

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Biochem Pharmacol; 31(11):2077-2082 1982

Four strains of guinea pigs (Hartley, No 2, No 13 and JY-1) were examined for the effects of ip treatment with 3-methylcholanthrene on aryl hydrocarbon hydroxylase activity, total cytochrome P-450 content in liver and lung microsomes, and NADPH-cytochrome c reductase activity in liver microsomes. Following treatment with 3-methylcholanthrene at a dose of 50 mg/kg body wt, aryl hydrocarbon hydroxylase activity and cytochrome P-450 content in liver were both increased in all the strains used, and the activity of NADPH-cytochrome c reductase in liver was also increased in all strains except No 13. While the cytochrome P-450 content in lung was increased in all the strains except No 13, there was no increase in the aryl hydrocarbon hydroxylase activity in lung from any strain of guinea pig examined. When the dose of 3-methylcholanthrene was increased to 250 mg/kg body wt, an apparent induction of aryl hydrocarbon hydroxylase was detected in the lung from the Hartley strain of guinea pigs, but not in the other three strains. In summary, marked differences were seen in sensitivity to 3-methylcholanthrene between liver and lung, and apparent strain differences were observed among the guinea pigs used in this experiment. (Author abstract) (29 Refs)

78. COMPETITIVE HYDROCARBON INDUCTION OF AHH IN C3H/10T1/2 CELLS (MEETING ABSTRACT).

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Proc Am Assoc Cancer Res; 23:325 1982

We are studying the relative abilities of benz(a)anthracene (BA), 3-methylcholanthrene (3MC) and TCDD (2,3,7,8-tetrachlorodibenzoparadioxin) to induce cyt-P450 dependent benzo(a)pyrene metabolism (AHH (arylhydrocarbon hydroxylase)) in cultures of transformable C3H/10T1/2 mouse embryo fibroblasts. BA was found to be the most effective inducer of the three compounds; 13 uM BA (24 hr exposure) elicited a 7-10 fold increase in AHH activity. 10-7M TCDD gave a 2-fold induction, and no AHH increase was seen after exposure of the cells to 13 uM 3MC. All three compounds markedly induced C3H mouse liver AHH activity. As we and others have reported, the extent of induction seen in the 10T1/2 cell cultures was dependent upon the degree of cell confluence. Increasing concentrations of 3MC were able to totally suppress the induction seen with 13 uM BA alone in a dose related manner. Significantly higher concentrations of 3MC were required to suppress the induction when 26 uM BA was added to the medium. Based on these data, 3MC may be acting as a competitive antagonist (without eliciting a 3MC agonist reponse) at a receptor which mediates BA induction in these cells, or 3MC metabolites may be sufficiently toxic in these cells to prevent a normal induction response. (no Refs)

79. LIVER NEOPLASIA AND INDUCTION OF HEPATIC MIXED FUNCTION OXIDASE ENZYMES IN THE RAINBOW TROUT FOLLOWING DIETARY EXPOSURE TO BENZO(A)PYRENE (MEETING ABSTRACT).

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Proc Am Assoc Cancer Res; 23:226 1982

The influence of benzo(a)pyrene (BP) on the induction of certain enzymes within the hepatic mixed function oxidase (MFO) system and its potential carcinogenicity were examined in rainbow trout during a continuous dietary exposure. Nine week feeding trials were performed using 500 and 1000 ppm of BP to determine the maximum tolerated dose (MTD) without producing fish mortalities or growth inhibition. Levels of MFO enzymes including ethoxyresorufin-O-deethylase (EROD), ethoxycoumarin-O-deethylase (ECOD), arylhydrocarbon hydroxylase (AHH) and cytochrome P-450 were measured during this time. A feeding trial using a MTD of 1000 ppm was initiated in duplicate groups of 100 fingerling rainbow trout. Trout were sampled at 6, 12 and 18 months for necropsy and subsequent gross and histological examination of internal organs. Mean MFO enzyme levels of EROD, ECOD, and AHH were significantly elevated showing dose and time response relationships when compared to those of fish fed a BP-free diet. P-450 levels in BP-fed fish increased only slightly. At 12 months 15% of the BP-fed fish had histologically confirmed neoplastic lesions of the liver. After 18 months 20% gross lesions were observed, histological confirmation is in progress. No evidence of neoplasia was observed in control fish. These results indicate that in rainbow trout BP is a potent inducer of certain hepatic MFO enzymes and is a hepatocarcinogen when fed continuously in the diet. (no Refs)

80. INDUCTION OF BENZO[A]PYRENE HYDROXYLASE IN SKIN AND LIVER BY CUTANEOUS APPLICATION OF JUTE BATCHING OIL.

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Toxicology; 23(4):347-352 1982

The ability of jute batching oil (JBO; two varieties) to pass through the skin, either metabolized or not; the biochemical changes in skin and liver following cutaneous exposure to JBO; and the duration of the effects in both tissues after a single painting were investigated. Female albino mice of ITRC strain were used in skin painting experiments and as sources of skin and liver tissue microsomal preparations. Cutaneous application of JBO for 8 days resulted in increased liver wt (35%) and hepatic microsomal protein content (30%). Benzo[a]pyrene hydroxylase (BAPH) activity in treated liver and skin was enhanced 2-and 10-fold, respectively, but hepatic aminopyrene demethylase activity was unaltered. Catalytically and spectrally distinct microsomal cytochrome P-448 levels were increased in hepatic and skin microsomes from animals treated with JBO. A single skin painting increased BAPH activity in skin and liver to its maximum after 1 and 2 days, respectively. The higher enzyme activity persisted up to 6 days in skin and up to 14 days in liver, thereafter declining more rapidly in skin than liver. JBO, by virtue of its ability to enhance BAPH activity locally in the skin at the site of contact or distantly in liver after passage through the blood seems to inadvertently stimulate the metabolism of its own components. This behavior may contribute electrophilic metabolites to the epidermis, subsequently leading to neoplastic transformation of the cells. (16 Refs)

81. THE ROLE OF METABOLISM IN 2-ACETYLAMINOFLUORENE (AAF) DEPENDENT ELEVATION OF HEPATIC EPOXIDE HYDROLASE (EH) ACTIVITY (MEETING ABSTRACT).

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Proc Am Assoc Cancer Res; 23:326 1982

Treatment of male rats with the hepatocarcinogen AAF causes substantial increases in hepatic microsomal EH activity. AAF is metabolized to N-hydroxy-2-acetylamino-fluorene (NOHAAF), which then can proceed either through sulfation or deacetylation pathways. These studies were designed to assess the role of the route of metabolism of AAF in elevating EH activity. Benzo(a)pyrene-4,5-oxide substrate was used to measure EH activity in post-mitochondrial supernatant prepared from the livers of male F-344 rats 48 hours after a single ip injection of AAF or NOHAAF. NOHAAF was found to be the more potent enhancer of EH activity, with an ED50 of 12 mg/kg vs 20 mg/kg for AAF. Pretreatment of male rats with Na2SO4 increased the EH response to 15 mg/kg NOHAAF (ED70) from 280% to 322% of control, while pretreatment with pentachlorophenol, an inhibitor of sulfotransferase, decreased the EH response to 220% of control. Pretreatment with bis(p-nitrophenyl)phosphate or isoniazid, inhibitors of deacetylation, caused no significant changes in the response to NOHAAF. None of the pretreatments alone had any effect on EH activity. Female CD rats have lower endogenous levels of sulfotransferase than female F-344 rats; treatment with 18 mg/kg NOHAAF raised EH levels to 391% of control in F-344 females but only 139% in CD females. (no Refs)

82. HALOGENATED BIPHENYLS AS AHH INDUCERS: EFFECTS OF DIFFERENT HALOGEN SUBSTITUENTS.

Bandiera S, Sawyer T, Campbell MA, Robertson L, Safe S
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Life Sci; 31(6):517-525 1982

The analogs 4'-iodo-2,3,4,5-tetrachlorobiphenyl, 4'-bromo-2,3,4,5-tetrachlorobiphenyl, 4'-chloro-2,3,4,5-tetrachlorobiphenyl and 4'-fluoro-2,3,4,5-tetrachlorobiphenyl were administered to immature male Wistar rats and the effects of this homologous series of 4'-halo-2,3,4,5-tetrachlorobiphenyls on the microsomal drug-metabolizing enzymes were determined. All the halogenated biphenyls increased microsomal benzo[a]pyrene hydroxylase (or aryl hydrocarbon hydroxylase, AHH), ethoxyresorufin (ER) O-deethylase and dimethylaminoantipyrine (DMAP) N-demethylase. The effects of the 4'-halo-2,3,4,5-tetrachlorobiphenyls on the microsomal enzyme activities and on the relative peak intensities and spectral shifts of the reduced cytochrome P-450:CO and ethylisocyanide (EIC) binding difference spectra were similar to those observed after coadministration of phenobarbitone (PB) and 3-methylcholanthrene (MC). The relative activities of the halogenated biphenyls were determined using two in vitro assays: namely cytochrome P-448 associated induction in rat hepatoma H-4-II E cells in culture and competitive binding to the hepatic cytosolic Ah receptor protein from male Wistar rats. The relative potencies of the 4'-halo-2,3,4,5-tetrachlorobiphenyls followed the order I greater than Br greater than Cl greater than F for both assays and differences in the EC50 values for the iodo and fluoro analogs were greater than three orders of magnitude for ER O-deethylase induction in rat hepatoma cells in culture. One possible explanation for these effects may be associated with differences in the polarizability of the laterally substituted halogen groups. However, other differences in the physico-chemical properties of the halogen atoms may also be important. (27 Refs)

83. RESPONSIVENESS OF CARMUSTINE (BCNU) TREATED MICE TO INDUCTION AND INHIBITION OF MIXED FUNCTION OXYGENASES.

Wilson VL, Larson RE
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Res Commun Chem Pathol Pharmacol; 36(3):439-448 1982

The responsiveness of (carmustine) BCNU treated mice to phenobarbital (Pb) induction of hepatic microsomal mixed function oxygenase (MFO) activity was studied. BCNU (30 mg/kg ip) produced significant (p less than 0.05) decreases in cytochrome P-450, total ethylmorphine metabolism (TEM) and ethylmorphine N-demethylase (EMN) by 21 days after treatment. The specific activities of TEM and EMN were decreased more than was P-450 content. Benzpyrene hydroxylase (BPH) was increased and 7-ethoxycoumarin O-deethylase (ECD) was unaffected at this time. Pb induction beginning on Day 17 after BCNU treatment resulted in a greater inductive response in the BCNU treated mice than in controls. The specific activities of all MFO enzymes studied were more markedly affected than were the raw activities suggesting activation. However, the responsiveness of the MFOs to the actions of inhibitors was not markedly influenced by BCNU pretreatment. (Author abstract) (16 Refs)

84. VINYLIDENE CHLORIDE: ITS METABOLISM BY HEPATIC MICROSOMAL CYTOCHROME P-450 IN VITRO.

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Biochem Pharmacol; 31(11):2083-2092 1982

The effects of inducing agents on the binding and metabolism of vinylidene chloride by hepatic microsomal cytochrome P-450 are reported. Hanes plots for the Type I binding of vinylidene chloride to cytochrome P-450 were biphasic with hepatic microsomes from untreated and beta-naphthoflavone or phenobarbital-treated male rats. Neither pretreatment affected the value of the Ks for the high-affinity binding site for vinylidene chloride, while phenobarbital induction, but not beta-naphthoflavone treatment, decreased the value of the Ks for the low-affinity site by three-fold. It is concluded that multiple forms of cytochrome P-450 bind and metabolize vinylidene chloride. However, the form of the enzyme elevated by phenobarbital plays, at most, a minor role in these processes, while the form induced by beta-naphthoflavone is not involved in either process. The effect of metabolism of vinylidene chloride by cytochrome P-450 on the relationship between the metabolism and toxicity of vinylidene chloride in vivo and its mutagenicity in vitro is considered. (37 Refs)

85. SEQUENTIAL ADMINISTRATIONS OF POLYRIBOINOSINIC ACID AND POLYCYTIDYLIC ACID INDUCE INTERFERON AND DEPRESS THE HEPATIC CYTOCHROME P-450-DEPENDENT MONOOXYGENASE SYSTEM.

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Biochem Biophys Res Commun; 106(3):947-952 1982

Injection of 5 mg of single stranded polyriboinosinic acid/kg body wt into male Swiss Random mice followed 1 hr later by injection of 5 mg of single stranded polyribocytidylic acid/kg resulted in losses of ethylmorphine N-demethylase activity and cytochrome P-450 similar to those elicited by 10 mg/kg of double stranded polyriboinosinic.polyribocytidylic acid. Large serum interferon levels were observed after administration of the single-stranded compounds in the same order. When the order was reversed, neither of these effects were observed. (19 Refs)

ALTERATION OF OTHER CARCINOGEN-METABOLIZING ENZYMES BY CARCINOGENS

86. EFFECT OF MICROSOMALLY ACTIVATED AFB1 ON GGT ACTIVITY IN 3 RAT LIVER CELL LINES.

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Br J Cancer; 45(6):945-952 1982

Three cell lines derived from adult rat liver have been used to study changes in levels of gamma-glutamyltransferase (GGT), a possible marker for premalignant transformation in liver in vivo. None of the cell lines was able to metabolize aflatoxin B1 (AFB1) and treatment with AFB1 alone did not influence GGT activity. However, treatment with microsomally activated AFB1 increased the level of activity in a cell line (BL8L) derived from normal liver with very low levels of GGT, by as much as 10-fold, and 5-fold in a cell line (ARL) also isolated from normal rat liver, but which had subsequently undergone spontaneous transformation. Microsomes from rats pretreated with phenobarbitone were compared with those from 3-methylcholanthrene-treated animals. AFB1 activated by the former produced larger increases in GGT activity, but in no case did the enzyme levels approach that in a cell line (JBI) derived from a hepatoma in the liver of an AFB1-fed rat. Treatment of JBI cells with microsomally activated AFB1 produced no further increase in activity. Histochemical staining indicated an uneven distribution of enzyme in all cell populations, both before and after treatment. This cell-culture system is useful for further studies on the role of GGT in carcinogenesis. (Author abstract) (26 Refs)

87. LYSOSOMAL ISOZYME PATTERNS IN ETHYLNITROSOUREA-INDUCED BRAIN TUMORS.

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Eur J Cancer Clin Oncol; 18(5):463-469 1982

Isozyme patterns for five acid hydrolases, acid phosphatase (AP), aryl-sulfatase (AS), beta-glucuronidase (beta-Glu), N-acetylglucosaminidase (NAG) and beta-galactosidase (beta-Gal), were studied in isolated lysosomes from ethylnitrosourea (ENU)-induced gliomas and compared with normal and newborn rat brains. With polyacrylamide gel electrophoresis (PAGE), AP was separated into three bands, acidic (A), intermediate (B) and basic (C). In tumors and newborn brains there was a decrease in A and C but a significant increase in B. For NAG the acidic form was elevated by 9-19% in tumors, while newborn brains showed a 19% decrease. Even though the band intensities of beta-Glu in tumors and newborn brains were increased, the relative distribution remained similar to normal brain. With isoelectric focusing, five hydrolases were separated into four to five distinct forms. In ENU-induced gliomas the intensities of all peaks were considerably increased, but in most cases the number of isozymes remained the same. In tumors the isoelectric points were shifted towards the acidic side and smaller peaks in the basic regions merged into more acidic peaks. This effects was especially evident for AP and Gal. In the cases of AS, beta-Glu and NAG, consistently more activity was associated with acidic peaks than with the basic ones. Our data indicates that there is a significant increase in acidic forms of some of the lysosomal hydrolases studied in ENU-induced brain tumors. (Author abstract) (30 Refs)

88. INDUCTION OF SPERMIDINE N(1)-ACETYLTRANSFERASE BY DIALKYLNITROSAMINES.

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Cancer Res; 42(8):2990-2995 1982

Treatment of rats with dimethylnitrosamine (30 mg/kg) or diethylnitrosamine (200 mg/kg) produced a rapid increase in the activity of spermidine N1-acetyltransferase which peaked at values seven-fold greater than did control at 6 hr after exposure. This increase led to a small accumulation of N1-acetylspermidine in the liver but produced a more striking effect on putrescine which increased 30-to 40-fold after 2 days. Most of this increase appeared to be due to the conversion of N1-acetylspermidine into putrescine which is catalyzed by polyamine oxidase. Treatment with the nitrosamines also increased the conversion of spermine into spermidine which replaced the spermidine converted into putrescine. Spermine levels were therefore significantly depressed by treatment with these carcinogens. These results indicate that these hepatocarcinogens bring about an increase in putrescine and in the spermidine/spermine ratio in the liver not only by enhancement of ornithine decarboxylase but also by induction of the spermidine N1-acetyltransferase activity which is the rate-limiting step in the acetylase-oxidase pathway for interconversion of the polyamines. (Author abstract) (35 Refs)

89. CLONAL GROWTH OF CARCINOGEN-INDUCED ENZYME-DEFICIENT PRENEOPLASTIC CELL POPULATIONS IN MOUSE LIVER.

Rabes HM, Bucher T, Hartmann A, Linke I, Dunnwald M
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Cancer Res; 42(8):3220-3227 1982

The cellular origin of preneoplastic subpopulations in liver during chemical carcinogenesis has not yet been clarified. An experimental approach to this problem became possible by using female phenotypic mosaics caused by the X-chromosome inactivation ('lyonization') occurring early in embryogenesis. Allozymes of the X-linked enzyme phosphoglycerate kinase (PGK-1) served as markers of the maternal (wild-type PGK-1B) and paternal (variant PGK-1A) X-chromosomes in crosses of near-congenic C3H mice. These PGK allozymes are of similar activity and stability but can be separated electrophoretically and quantified by a fluorimetric method. Pgk-1a/Pgk-1b heterozygous females were subjected to chronic 2-acetylaminofluorene feeding for up to 14 mo. Phenotypic expression of PGK-1B and PGK-1A was determined in ug samples as well as in mg samples of liver and other organs. Samples of adenosine triphosphatase-deficient preneoplastic populations punched out from cryostat serial sections of liver of 2-acetylaminofluorene-fed mice disclosed a PGK allozyme pattern strikingly different from the norm. Thirty-nine of 40 preneoplastic nodules contained a pure population of either PGK-1A or PGK-1B expressing cells. Mean contamination by the opposite PGK type was 1.1%. In all cases, the PGK expression in the preneoplastic nodules differed from the surrounding liver parenchyma. Only a single large hyperplastic nodule was composed of several subpopulations with respect to PGK expression. Determination in normal liver tissue of the patch size of coherent populations with a homogeneous expression of one PGK allozyme revealed an av of about eight hepatocytes per patch. Each microsample used for PGK determinations consisted of an av of 25 patches. It is evident from these results that AAF-induced, ATPase-deficient preneoplastic subpopulations in the mouse

liver are in all probability clones derived from a single cell. (Author abstract) (43 Refs)

90. INDUCTION OF HEPATOCELLULAR NUCLEOSIDE-5'-TRIPHOSPHATASE (ATPASE) DEFICIENT FOCI BY VINYL CHLORIDE (VC) (MEETING ABSTRACT).

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International Agency for Research on Cancer, 69372 Lyon Cedex 2, France
Proc Am Assoc Cancer Res; 23:231 1982

In many species including man, VC induces angiosarcomas originating from endothelial cells of the liver, while in newborn rats, hepatocytes are more susceptible. This effect can be quantified by evaluating preneoplastic hepatocellular foci with ATPase deficiency. Rats were exposed to 2000ppm VC (8hrs/day), either transplacentally (schedule A) or immediately after birth for different time intervals (B-E), and from the age of 21 days onwards (F). Four-month old animals were sacrificed and the livers evaluated histochemically for ATPase deficient foci. Transplacental exposure (A) and schedule B revealed no increase in ATPase deficient foci, possibly due to the low rate of VC metabolism at this developmental stage. The % foci increased from schedule C to D but was not further enhanced after prolonged exposure (E). Only a few ATPase deficient foci were observed when exposure started 21 days after birth (F). As shown previously, a 70 day exposure of adult female rats to VC also did not result in ATPase deficient foci. These results indicate that the initiation of preneoplastic lesions of VC in rat hepatocytes is restricted to the early lifetime and that VC does not exert a substantial growth-promoting effect on induced ATPase deficient foci. (1 Ref)

BIOASSAY BASED UPON ACTIVATION

91. AN EVALUATION OF ASSAY PROCEDURES FOR DETECTION OF TUMOR PROMOTORS.

Sivak A
(c/o P. H. Lohman) Medical Biological Lab. TNO, P.O. Box 45, 2280 AA Rijswijk, The Netherlands
Mutat Res; 99(3):377-387 1982

Direct cell culture assays, direct animal assays, and indirect assays for detection of tumor promoters are reviewed. Among the biological assays available for detection of tumor-promoting agents by means others than long-term carcinogenicity tests, those procedures that can determine phorbol ester activity and other substances active on mouse skin have been studied most intensively. When fibroblast cultures derived from individuals with hereditary adenomatosis of the colon and the rectum were treated with phorbol myristate acetate (PMA), they yielded cultures that could grow in soft agar and produce tumors in the anterior chamber of the eye of athymic mice. Experiments with oncogenic viruses and phorbol esters in cell culture systems show that phorbol esters can influence the neoplastic phenotype resulting from biological oncogenic as well as chemical stimuli. An enhancement of mutation frequency in V79 Chinese hamster cells was observed in cell culture with phorbol ester. PMA and other phorbol esters could reduce the recovery of 6-thioguanine-resistant mutants in a mixed culture of V79 cells in the presence of this purine derivative. A range of substances including promoters for rat liver (chlorinated aromatics), rat bladder (saccharin), and other organs also have been reported to have a blocking effect on metabolic cooperation. Studies indicated that the biochemical responses not directly implied in a causal manner to tumor promotion would require substantial validation to establish their usefulness as screening tools for tumor-promoting agents. (62 Refs)

92. DNA REPAIR ASSAYS AS TESTS FOR ENVIRONMENTAL MUTAGENS. A REPORT OF THE U.S. EPA GENE-TOX PROGRAM.

Larsen KH, Brash D, Cleaver JE, Hart RW, Maher VM, Painter RB, Sega GA
Environmental Mutagen Information Center, Oak Ridge Natl. Lab., Oak Ridge, TN, 37830
Mutat Res; 99(3):297-318 1982

Repair replication (RR) assayed in isopycnic gradients, RR measured by benzoylated naphthoylated diethylaminoethyl (BND) cellulose, RR assayed by bromodeoxyuridine (BUdR) photolysis, alkaline elution assays, repair of single-strand breaks measured in alkaline sucrose gradients, and loss of adducts from DNA are reviewed. BND cellulose chromatography has not been widely adopted for measurement of RR, despite its relative ease and the fact that multiple samples can be processed simultaneously. The BUdR photolysis method is better suited for screening than most of the other DNA repair assays; it can be well controlled using internal standards, and, if standard repair intervals are used, produces data suitable for precise quantitative comparisons. Alkaline elution appears to be useful for identification of DNA-damaging agents if appropriate quantification is performed; it is sensitive, easy to perform and analyze, applicable both in vivo and in vitro studies, and could be used for simultaneous processing of multiple samples. The alkaline sucrose gradient technique for determining DNA repair appears to have limited usefulness for hazard evaluation. The chemicals tested in the various DNA repair assays are listed in the summary table with chemical classifications, and, where available, carcinogenicity assessments. Most of the chemicals used were known inducers of DNA damage and repair, and known mutagens and carcinogens. Of the 49 compounds listed, 23 are alkylating agents, and an additional 11 are polycyclic aromatic hydrocarbons. On theoretical grounds, evidence of DNA repair is a poor indicator of genetic risk. Thus, risk assessment based on repair data must be highly speculative. (130 Refs)

93. AN EVALUATION OF THE HOST-MEDIATED ASSAY AND BODY FLUID ANALYSIS. A REPORT OF THE U.S. ENVIRONMENTAL PROTECTION AGENCY GENE-TOX PROGRAM.

Legator MS, Bueding E, Batzinger R, Connor TH, Eisenstadt E, Farrow MG, Ficsor G, Hsie A, Seed J, Stafford RS
Dept. Preventive Medicine and Community Health, Div. Environmental Toxicology, Univ. Texas Medical Branch, Galveston, TX, 77550
Mutat Res; 99(3):319-374 1982

Host-mediated assay (HMA) and body fluid analysis (BFA) are reviewed. The HMA is capable of detecting diverse groups of chemical mutagens by making use of a wide range of indicator systems. Chemicals requiring metabolic activation (including non-hepatic activation) are rendered biologically active mutagens by the host animal. Furthermore, these active metabolites of the administered chemicals are able to come in contact with the indicator, which is usually located in the peritoneal cavity. The immunological system of the host may alter the integrity of the indicators so that the mutagenic response is altered. Of 206 chemicals that were evaluated in the HMA, 133 were mutagenic with one or more indicators. BFA in animals can provide useful information on the in vivo formation of mutagenic substances and can be used to identify exposure to mutagens in man. The limit of BFA, in terms of both method and predictive value, have not been assessed. The value of pretreating test fluids with deconjugated enzymes is uncertain. While a positive result obtained after enzymatic hydrolysis of conjugates indicates that mutagenic species are being generated in vivo, the presence of conjugates is also indicative of the capability of in vivo defense mechanisms to detoxify these agents, although a few exceptions may exist. Thus, false-positive responses could be obtained. Results of BFA could be more indicative of genetic risk than results from strictly in vitro tests. (193 Refs)

94. HYDROGEN ION DYNAMICS AND CANCER: AN APPRAISAL.

Harguindey S

Dept. Thoracic Surgery and Oncology, Roswell Park Memorial Inst., 666 Elm St., Buffalo, NY, 14263

Med Pediatr Oncol; 10(3):217-236 1982

The concentration of hydrogen ions plays a critical role in all biochemical processes, including multiple enzymatic reactions and in the regulation of metabolism. The acid-base aspects of metabolism as applied to cancer are considered. Preliminary data are presented. The primary concept of hydrogen ion dynamics is related to prevention, development, and etiology of carcinogenicity, as well as to the regression of certain malignant tumors. The present overview summarizes, in terms of H+ dynamics, many related concepts in oncologic research and associates and integrates a variety of basic and clinical observations toward better understanding of cancer cell behavior, biology, and host-tumor relationships. (Author abstract) (209 Refs)

REVIEWS AND OTHER RELEVANT STUDIES

95. MOLECULAR EPIDEMIOLOGY AND CARCINOGEN-DNA ADDUCT DETECTION: NEW APPROACHES TO STUDIES OF HUMAN CANCER CAUSATION.

Perera FP, Weinstein IB

Div. Environmental Sciences, Columbia Univ., New York, NY, 10032

J Chronic Dis; 35(7):581-600 1982

Techniques with potential usefulness in molecular cancer epidemiology are reviewed, with special emphasis placed upon a highly sensitive assay that detects covalent binding of the polycyclic aromatic hydrocarbon benzo(a)pyrene to human DNA. Benzo(a)pyrene has assumed considerable importance among chemical carcinogens because it has proven carcinogenic potency in a variety of species and tissues, it is ubiquitous in the environment, and there is extensive information regarding its metabolism and mode of action. Laboratory methods applicable to molecular cancer epidemiology include techniques to assess specific host factors that may influence susceptibility to carcinogens; assays that detect carcinogens in human tissues, cells, or fluids; assays at the cellular level of biologically effective doses of carcinogens; and methods to measure early biologic and biochemical responses to carcinogenic agents. Inherited and acquired host factors that may influence human susceptibility to carcinogens, methods for detecting and quantitating chemical carcinogens in human tissues or body fluids, markers for assessing the biologically effective dose of carcinogens in humans, potential markers for early biological and biochemical response to carcinogens in humans, and the immunoassay of benzo(a)pyrene-DNA adducts as an example of a promising marker in molecular cancer epidemiology are among topics discussed. (229 Refs)

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CHARLES HEIDELBERGER University of Southern California	*Mutagenesis and Oncogenic Transformation of Mouse Embryo Cells*	#VK04 54 min.
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CHEMICAL CARCINOGENESIS

1. ASBESTOS CARCINOGENESIS: ASBESTOS INTERACTIONS AND EPITHELIAL LESIONS IN CULTURED HUMAN TRACHEOBRONCHIAL TISSUES AND CELLS.
Haugen A, Harris C
Div. Cancer Cause and Prevention, NCI, Bethesda, MD
Recent Results Cancer Res; 82:32-42 1982

2. REVIEW: ORAL CONTRACEPTIVES AND MENOPAUSAL ESTROGENS IN RELATION TO BREAST NEOPLASIA.
Brzezinski A, Schenker JG
Dept. Obstetrics and Gynecology, Hadassah Univ. Hosp., POB 12000, 91120 Jerusalem, Israel
Isr J Med Sci; 18(4):433-438 1982

3. LIVER DISEASES DUE TO HORMONAL CONTRACEPTIVES.
Lie TS
Chirurgische Klinik und Poliklinik, Universitat, Sigmund-Freud-Str. 25, D-5300 Bonn 1, W. Germany
MMW; 124(20):489-494 1982
In GER

RADIATION CARCINOGENESIS

4. THE WORK OF THE NRPB 1977/80 AND A REVIEW OF THE FIRST 10 YEARS.
National Radiological Protection Board
Natl. Radiological Protection Board, Chilton, Didcot, Oxfordshire OX11 0RQ, England
The Work of the NRPB 1977/80 and a Review of the First 10 Years. Chilton, Didcot, Oxfordshire, National Radiological Protection Board, 70 pp., 1981.

DIETARY FACTORS IN CARCINOGENESIS

5. ALCOHOL AND CARCINOGENESIS.
Seitz HK, Czygan P, Kommerell B
Schwerpunkt Gastroenterologie, Medizinische Universitatsklinik, Bergheimer Str. 58, D-6900 Heidelberg 1, W. Germany
Leber Magen Darm; 12(3):95-107 1982
In GER

6. ZINC, COPPER, AND MANGANESE IN IMMUNE FUNCTION AND EXPERIMENTAL ONCOGENESIS.
Beach RS, Gershwin ME, Hurley LS
Dept. Internal Medicine, Div. Rheumatology-Clinical Immunology, Univ. Calif., Davis, CA, 95616
Nutr Cancer; 3(3):172-191 1982

EPIDEMIOLOGY, ETIOLOGY AND GENETIC ASPECTS OF HUMAN CANCER

7. TRENDS IN CANCER INCIDENCE: CAUSES AND PRACTICAL IMPLICATIONS. PROCEEDINGS OF A SYMPOSIUM HELD OSLO, NORWAY, 6-7 AUGUST 1980.
Magnus K
The Cancer Registry Norway, Montebello, Oslo 3, Norway
Trends in Cancer Incidence: Causes and Practical Implications, Proceedings of a Symposium held Oslo, Norway, 6-7 August 1980. Washington, D. C., Hemisphere Publishing Corporation, 446 pp., 1982.

ENVIRONMENTAL AND OCCUPATIONAL FACTORS IN CARCINOGENESIS

8. QUANTIFICATION OF OCCUPATIONAL CANCER.
Peto R, Schneiderman M
Nuffield Dept. Clinical Medicine, Radcliffe Infirmary, Univ. Oxford, Oxford, England
Banbury Rep (9): 756 pp., 1981.

9. NASAL CARCINOMA IN WOODWORKERS: A REVIEW.
Wills JH
Sch. Medicine, Uniformed Services Univ. Health Sciences, 4301 Jones Bridge Road, Bethesda, MD, 20814
JOM; 24(7):526-530 1982

10. AIR POLLUTION AND CANCER. A REVIEW OF EXPERIMENTAL INVESTIGATIONS.
Madsen ES, Nielsen PA, Pedersen JC
(c/o Nielsen), Stigardsvej 2, DK-2900 Hellerup, Denmark
Ugeskr Laeger; 144(23):1719-1721 1982
In DAN

11. AIR POLLUTION AS A RISK FACTOR IN LUNG CANCER.
Vena JE
Dept. Social and Preventive Medicine, State Univ. New York at Buffalo, 2211 Main St., Buffalo, NY, 14214
Am J Epidemiol; 116(1):42-56 1982

12. INHALATION CARCINOGENESIS: AN OVERVIEW.
Chretien J
Hopital Laennec, 42 rue de Sevres, F-75007 Paris, France
Recent Results Cancer Res; 82:1-10 1982

13. THE NITROSAMINE HAZARD.
Yonkers AJ
Dept. Otolaryngology, Univ. Nebraska, Omaha, NE
Ear Nose Throat J; 61(7):407-414 1982

CELLULAR AND MOLECULAR MECHANISMS IN CARCINOGENESIS

14. ONCOGENES OF SPONTANEOUS AND CHEMICALLY INDUCED TUMORS.
Weinberg RA
Center for Cancer Res., Massachusetts Inst. Technology, Cambridge, MA, 02139
Adv Cancer Res; 36:149-163 1982

15. RELATIONSHIP OF DNA TERTIARY AND QUATERNARY STRUCTURE TO CARCINOGENIC PROCESSES.
Lipetz PD, Galsky AG, Stephens RE
Dept. Radiology, Ohio State Univ., Columbus, OH, 43210
Adv Cancer Res; 36:165-210 1982

16. ROLE OF ENZYMATIC METHYLATION OF DNA IN CELL DIFFERENTIATION AND TRANSFORMATION.
Fedorov NA
Central Res. Inst. Hematology and Blood Transfusion, Moscow, USSR
Eksp Onkol; 4(3):3-11 1982
In RUS

17. HYDROGEN ION DYNAMICS AND CANCER: AN APPRAISAL.
Harguindey S
Dept. Thoracic Surgery and Oncology, Roswell Park Memorial Inst., 666 Elm St., Buffalo, NY, 14263
Med Pediatr Oncol; 10(3):217-236 1982

MODIFICATION OF CARCINOGENESIS

18. CARCINOGENESIS AND BIOLOGICAL EFFECTS OF TUMOR PROMOTERS.
Hecker E
Inst. Biochemistry, German Cancer Res. Center, Heidelberg, W. Germany
Carcinogenesis 7: 664 pp., 1982.

VIRAL AND IMMUNOLOGICAL ASPECTS OF CARCINOGENESIS

19. AVIAN LEUKEMIA VIRUSES: ONCOGENESES AND GENOME STRUCTURE.
Graf T, Stehelin D
Inst. Virology, German Cancer Res. Center, In Neuenheimer Feld 280, 6900 Heidelberg, W. Germany
Biochim Biophys Acta; 651(4):245-271 1982

20. HYPERPLASTIC AND NEOPLASTIC ERYTHROPROLIFERATIVE DISEASES INDUCED BY ONCOGENIC MURINE RETROVIRUSES.
Scolnick EM
Lab. Tumor Virus Genetics, NCI, Bethesda, MD, 20205
Biochim Biophys Acta; 651(4):273-283 1982

METHODOLOGY IN CARCINOGENESIS RESEARCH

21. MOLECULAR EPIDEMIOLOGY AND CARCINOGEN-DNA ADDUCT DETECTION: NEW APPROACHES TO STUDIES OF HUMAN CANCER CAUSATION.
Perera FP, Weinstein IB
Div. Environmental Sciences, Columbia Univ., New York, NY, 10032
J Chronic Dis; 35(7):581-600 1982

22. AN EVALUATION OF ASSAY PROCEDURES FOR DETECTION OF TUMOR PROMOTORS.
Sivak A
(c/o P. H. Lohman) Medical Biological Lab. TNO, P.O. Box 45, 2280 AA Rijswijk, The Netherlands
Mutat Res; 98(3):377-387 1982

23. DNA REPAIR ASSAYS AS TESTS FOR ENVIRONMENTAL MUTAGENS. A REPORT OF THE U.S. EPA GENE-TOX PROGRAM.
Larsen KH, Brash D, Cleaver JE, Hart RW, Maher VM, Painter RB, Sega GA
Environmental Mutagen Information Center, Oak Ridge Natl. Lab., Oak Ridge, TN, 37830
Mutat Res; 98(3):287-318 1982

24. AN EVALUATION OF THE HOST-MEDIATED ASSAY AND BODY FLUID ANALYSIS. A REPORT OF THE U.S. ENVIRONMENTAL PROTECTION AGENCY GENE-TOX PROGRAM.
Legator MS, Bueding E, Batzinger R, Connor TH, Eisenstadt E, Farrow MG, Ficsor G, Hsie A, Seed J, Stafford RS
Dept. Preventive Medicine and Community Health, Div. Environmental Toxicology, Univ. Texas Medical Branch, Galveston, TX, 77550
Mutat Res; 98(3):319-374 1982

25. THE PHYSIOLOGICAL IMPORTANCE OF THE COLONIC MICROFLORA.
Gustafsson BE
Dept. Germfree Res., Karolinska Inst., Box 60 400, S-104 01 Stockholm, Sweden
Scand J Gastroenterol [Suppl]; 17(77):117-131 1982

26. AN ASSESSMENT OF THE ROLE OF MICRODOSIMETRY IN RADIOBIOLOGY.
Goodhead DT
Medical Res. Council Radiobiology Unit, Harwell, Didcot OX11 0RD, England
Radiat Res; 91(1):45-76 1982

OTHER REVIEWS IN CARCINOGENESIS

27. PSYCHOSOCIAL ASPECTS OF CANCER.
Cohen J, Cullen JW, Martin LR
Sch. Social Welfare, Univ. California, Los Angeles, Los Angeles, CA
Psychosocial Aspects of Cancer. New York, Raven Press, 320 pp., 1982.

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MECHANISMS OF CARCINOGENESIS

Activation and Metabolism of Carcinogens

SERIES CK08 No. 82/12

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METABOLIC ACTIVATION OF CARCINOGENS

1. HYDROXYLATION AND ACTIVATION OF CARCINOGENS BY HUMAN COLON AND HUMAN COLON TUMOR CELLS (MEETING ABSTRACT).

Newaz SN, Fang WF, Strobel HW
The University of Texas Medical School, Houston, TX, 77025
Fed Proc; 41(3):1564 1982

Microsomes prepared from human colons obtained at autopsy catalyze the hydroxylation of benzo[a]pyrene (BAP) and 1,2-dimethylhydrazine (DMH). The metabolism of DMH was highest in microsomes prepared from the descending colon, intermediate in the transverse colon and lowest in the ascending colon. The metabolism of BAP does not show such an anatomical distribution. Human colon tumor cell line LS174T microsomes also catalyze the hydroxylation of DMH and BAP in an inducible manner. Phenobarbital/hydrocortisone (P/H) induces DMH hydroxylation 3-fold and BAP hydroxylation 10-fold. Benzanthracene (BA) induces BAP hydroxylation 30-fold indicating that these cells have a mixed function oxidase system. Cyclophosphamide (CP) is also hydroxylated to its cytotoxic metabolite by the colon tumor cells as judged by a

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HE 20.3173/2 :

33% decrease in cell number. BA induces cyclophosphamide activation and cell killing by 80%, while P/H effects a 76% decrease in cell number as compared with controls. These results show that human colon and human colon tumor cells are totipotent for activation of carcinogens and the antitumor agent cyclophosphamide. (no Refs)

2. THE ROLE OF L-REGION METHYL SUBSTITUENTS IN THE METABOLIC ACTIVATION OF THE POTENT CARCINOGEN, 7,12-DIMETHYLBENZ(A)ANTHRACENE (DMBA).

Watabe T, Ishizuka T

Lab. Drug Metabolism and Toxicology, Dept. Hygienic Chemistry, Tokyo Coll. Pharmacy, 1432-1 Horinouchi, Hachioji, Tokyo 192-03, Japan

J Pharmacobio Dyn; 5(5):S-57 1982

7-Hydroxymethyl-12-methylbenz(a)anthracene and 12-hydroxymethyl-7-methylbenz(a)anthracene, major carcinogenic products of 7,12-dimethylbenz(a)anthracene, were activated more potently by cytosolic sulfotransferase than by microsomal monooxygenase as measured by the Ames assay. These data suggest that the sulfate ester conjugation of these derivatives plays a more important role in their activation than does microsomal epoxidation. (no Refs)

3. STEREOSELECTIVE METABOLISM OF BENZ[A]ANTHRACENE (BA) TO (+)-BA (5S,6R)-OXIDE BY A HIGHLY PURIFIED AND RECONSTITUTED SYSTEM CONTAINING CYTOCHROME P-450C (MEETING ABSTRACT).

Van Bladeren PJ, Armstrong RN, Cobb D, Ryan DE, Thomas PE, Levin W, Jerina DM

National Institutes of Health, Bethesda, MD, 20205

Fed Proc; 41(3):1222 1982

A principal site of metabolism of BA by liver microsomes from 3-methylcholanthrene-treated rats is the K-region 5,6-double bond. In order to determine the absolute configuration of the 5,6-arene oxide formed, a procedure has been developed to separate the four possible isomeric glutathione conjugates (two positional isomers from each enantiomer) which were obtained synthetically from the individual enantiomeric arene oxides. When [14C]-BA was incubated with a highly purified and reconstituted monooxygenase system containing cytochrome P-450c (greater than 70% of total cytochromes P-450 in liver microsomes from 3-methylcholanthrene-treated rats) and glutathione was allowed to react with the arene oxides formed, HPLC (high pressure liquid chromatography) of the resultant adducts indicated that radioactive conjugates were formed only from the (+)-(5S,6R)-enantiomer. Insignificant amounts of adducts (less than 3%) from the opposite enantiomer were detectable. The present results as well as previous studies which established that cytochrome P-450c predominantly forms benzo[a]pyrene (4S,5R)-oxide from benzo[a]pyrene are in agreement with our theoretical predictions of the steric requirements of the catalytic binding site of cytochrome P-450c. (no Refs)

4. THE METABOLISM OF DIBENZ(A,H)ANTHRACENE (DBA) BY MOUSE HEPATIC MICROSOMES AND ITS RELATIONSHIP TO DBA INDUCED TUMOR FORMATION (MEETING ABSTRACT).

Lubet RA, Connolly G, Nebert DW, Kouri RE

Division of Toxicology and Oncology, Microbiological Associates, Bethesda, MD, 20816

Fed Proc; 41(3):1426 1982

DBA metoblism by MCA (monoclonal antibodies) induced hepatic microsomes from four strains of mice (C57Bl/6J, C3H/HeJ, AKR/J and DBA/2J) was determined employing reverse phase HPLC (high pressure liquid chromatography) analysis. Strains C3H/HeJ and C57Bl/6 showed a three to six fold higher rate of overall metabolism than strains AKR/J and DBA/2J. In addition these strains showed a five to nine fold greater rate of production of DBA 3,4 dyhydrodiol, the apparent precursor to the bay-region diol expoxide, reflecting a shift in metabolism to the 3,4 position in MCA induced microsomes. When DBA itself was employed to induce aryl hydrocarbon hydroxylase and Ethoxyresorufin O-deethylase activities in mice the C3H and C57Bl strains were induced while the AKR and DBA/2 were not. When animals from these strains were injected subcutaneously with 150 ug DBA in corn oil strains C3H and C57Bl/6 had tumor incidences of 84 and 53% respectively, while strains AKR and DBA/2 had incidences of less than 3%. Further studies involving determinations of the roles of substrate concentration and conjugation reactions in microsomal activation of DBA will be presented. (no Refs)

5. STEREOSELECTIVE METABOLISM OF THE (+)- AND (-)-ENANTIOMERS OF TRANS-1,2-DIHYDROXY-1,2-DIHYDROCHRYSENE TO BAY REGION 1,2-DIOL-3,4-EPOXIDES BY RAT LIVER ENZYMES (MEETING ABSTRACT).

Vyas KP, Yagi H, Tada M, Thakker DR, Ryan DE, Thomas PE, Conney AH, Levin W, Jerina DM

National Institutes of Health, Bethesda, MD. 20205

Fed Proc; 41(3):1222 1982

Metabolism of (+)- and (-)-chrysene 1,2-dihydrodiols was examined to establish whether the stereoselectivity of cytochrome P-450c toward these dihydrodiols parallels that observed for the corresponding phenanthrene 1,2-and B[a]P 7,8-dihydrodiols. Microsomes prepared from control and treated rats as well as a reconstituted system containing highly purified cytochrome P-450c stereoselectively metabolized (+)- and (-)-chrysene 1,2-dihydrodiols to their diastereomerically related bay-region 1,2-diol-3,4-epoxides. The extent to which diol epoxides were formed and the ratio of the two diastereomeric diol epoxides were highly dependent on both the enantiomer of the dihydrodiol and treatment of the rats. The trans diol epoxides predominated from the (-)-(1R,2R)-dihydrodiol and cis diol epoxide predominated from the (+)-enantiomer. Microsomes from 3-methylcholanthrene (3-MC)-treated rats displayed a higher degree of regio- and stereoselectivity compared to microsomes from control or phenobarbital (PB)-treated rats. In addition to diol epoxides, a phenolic metabolite was identified from both the (+)- and (-)-dihydrodiols. This phenolic-dihydrodiol was found to be an inhibitor of metabolism of the 1,2-dihydrodiol. Both PB and 3-MC failed to induce metabolism of the dihydrodiols per nmol cytochrome P-450. (no Refs)

6. CARCINOGENESIS BY ISOMERS OF N-NITROSO-3,5-DIMETHYLPIPERIDINE.

Lijinsky W, Reuber MD, Singer SS, Singer GM
Chemical Carcinogenesis Program, NCI-Frederick Cancer Res. Facility, Frederick, MD, 21701
JNCI; 68(6):989-991 1982

The cis- and trans-isomers of N-nitroso-3,5-dimethylpiperidine were administered separately in drinking water solution to groups of 20 female F344 rats for 50 weeks. The concentrations of the solutions were 0.72 mM for the cis-isomer and 0.14 mM for the trans-isomer. In both groups the animals died with tumors of the upper gastrointestinal (GI) tract, mainly carcinomas of the esophagus, at about the same time. A third group of animals was given a mixture of the two isomers in the ratio of 5 cis:1 trans, and these animals died more rapidly with the same upper GI tumors. The trans-isomer appeared to be a more potent carcinogen than the cis-isomer. The 3,5-dimethyl derivative is a less potent carcinogen than nitrosopiperidine. (Author abstract) (8 Refs)

7. EVIDENCE FOR A 2,3-EPOXIDE AS AN INTERMEDIATE IN THE MICROSOMAL METABOLISM OF 6-NITROBENZO(A)PYRENE (MEETING ABSTRACT).

Fu PR, Chou MW, Evans FE, Yang SK
National Center for Toxicological Research, Jefferson, AR, 72079
Fed Proc; 41(3):1730 1982

Nitrobenzo(a)pyrene (6-NO(2)-BaP), an environmental pollutant, was found to be metabolized by rat liver microsomes to form 1-and 3-hydroxy-6-NO(2)-BaP which were more mutagenic than 6-NO(2)-BaP tested in Salmonella typhimurium tester strains TA98 and TA100 with S9 activation. This study reports that this 3-hydroxy-6-NO2 metabolite is formed in vitro through a 2,3-epoxide intermediate which rearranges spontaneously via an NIH shift mechanism. The evidence was obtained by mass and 1H NMR (nuclear magnetic resonance) spectral analysis of the major metabolite, 3-hydroxy-6-NO(2)-BaP, of metabolism of 3-deutero-6-NO(2)-BaP by rat liver enzymes. These analyses indicated that 50% of the deuterium label was retained at the C-2 position. Thus, these results indicate that ring epoxidation by the cytochrome P-450 system is involved in the metabolism of 6-NO(2)-BaP. (no Refs)

8. DISTRIBUTION, ELIMINATION, AND TEST FOR CARCINOGENICITY OF 2,4-DINITROTOLUENE IN STRAIN A MICE.

Schut HA, Loeb TR, Stoner GD
Dept. Pathology, Medical Coll. Ohio, Toledo. OH, 43699
Toxicol Appl Pharmacol; 64(2):213-220 1982

The carcinogenicity of 2,4-dinitrotoluene (2,4-DNT) was reevaluated in terms of its ability to induce lung adenomas in strain A mice; tissue distribution and elimination were also studied following total ip doses of 600, 1,500, or 3,000 mg/kg of radiolabeled 2,4-DNT. The av number of lung tumors per mouse was not significantly different from that in vehicle-treated or untreated controls. After administration of 1, 10, or 100 mg/kg 2,4-DNT, excretion in urine was rapid, especially during the first hr, with 52.5, 60.1 and 67/0%, respectively, being eliminated within 4 hr. Early uptake in the large intestine was slight, blood concentration decreased with time, especially during the first hr after administration. At times earlier than 2 hr, levels in the liver were 2-to 4-fold higher than in the blood, whereas after 2 hr, the two compartments had comparable concentrations. A similar situation existed with respect to the kidney, except that higher levels than in the blood persisted up to 3 hr after administration. Elimination of radioactive material from the lungs ranged from 0.05-0.2% of the administered dose. Adipose tissue took up maximal levels amounting to 3.9-4.7% of the administered dose, whereas levels of 2,4-DNT in the brain, heart, and spleen were barely detectable and did not change with time and dose. The liver and small intestine seem to be the major sites of 2,4-DNT metabolism, which is virtually complete in these organs at 1 hr after ip administration. (23 Refs)

9. NITRATE AND NITRITE: ANALYSIS, PHARMACOKINETICS AND ENDOGENOUS SYNTHESIS.

Witter JP
The University of Wisconsin - Madison, Madison, WI
Diss Abstr Int [B]; 42(7):2712-B 1982

Nitrate and nitrite can react (spontaneously under acid conditions or through microbial metabolism) in the body with secondary amines to form the corresponding, carcinogenic N-nitroso compounds. Although nitrostable amines are present in every body compartment, knowledge of the presence of nitrosating sources (nitrite and nitrate) in the body is not as well understood. Using a short-lived isotope of nitrogen (13N), I observed that 13N-labeled nitrite and nitrate are absorbed from the gastrointestinal tract and are distributed to body compartments including the lower intestinal tract which previously was thought not to contain nitrate and nitrite. Labeled nitrite and nitrate are able to enter the lower intestinal tract by direct passage down the alimentary canal or by re-entry with various intestinal secretions. The chemical form of nitrite and nitrate in the intestinal tract of conventional-flora rats remains unknown but the bacterial flora is influential in their metabolism. Nitrate in germfree rats, on the other hand, is not metabolized while nitrite in germfree rats can be oxidized to nitrate. By the use of high performance liquid chromatographic technique for nitrate analysis in the feces and urine of germfree and conventional-flora rats, I determined that nitrate is formed endogenously in the rat body. Nitrate formation is due to host metabolism, not the microbial flora as previously suggested. On the basis of dietary supplementations during these nitrate balance studies and with the help of other data in the literature, I assembled a metabolic scheme that might account for endogenous nitrate formation in the rat. (no Refs)

10. 2-HALOACRYLIC ACIDS AS INDICATORS OF MUTAGENIC 2-HALOACROLEIN INTERMEDIATES IN MAMMALIAN METABOLISM OF SELECTED PROMUTAGENS AND CARCINOGENS.

Marsden PJ, Casida JE
(c/o Casida) Dept. Entomological Sciences, Univ. California, Berkeley, CA, 94720
J Agric Food Chem; 30(4):627-631 1982

The identity and amount of 2-haloacrylic acids excreted in the urine was studied in rats treated with 1,2-dibromo-3-chloropropane, tris(2,3-dibromopropyl) phosphate, octachlorodipropyl ether, and the herbicides sulfallate, diallate, and triallate. Determination of these acids is of interest in view of the fact that they may be the ultimate carcinogen of 2-chloroacrolein, which is a potent mutagen. (27 Refs)

OTHER METABOLISM OF CARCINOGENS

11. MECHANISMS CONTROLLING EXCRETION OF BENZO(A)PYRENE AND ITS METABOLITES BY THE SOUTHERN FLOUNDER, PARALICHTHYS LETHOSTIGMA (MEETING ABSTRACT).

Pritchard JB, Fresh ME, Bend JR, Niehs CV
Whitney Laboratory, St. Augustine, FL. 32084
Fed Proc; 41(3):1545 1982

Marine teleosts extensively metabolize polycyclic aromatic hydrocarbons (PAH) via the cytochrome P-450 mixed function oxidase system. In contrast to mammals, a much greater fraction, approximately 60%, of the metabolism of the model PAH, benzo(a)pyrene (BP), occurs at the benzo-ring. Metabolism in this region of the molecule yields metabolites which have been shown to be toxic, ie carcinogenic, mutagenic. Following injection of 2.5 umol/kg radiolabelled BP, BP-7-phenol, BP-1-phenol, or BP-7,8-trans-dihydrodiol, the clearance of each compound exceeded the simultaneously measured glomerular filtration rate, thus, demonstrated net tubular secretion. Clearance of label following BP-7,8-diol administration exceeded that following the phenol metabolites by 10 fold and was more than 30 times the initial clearance after injection of BP itself. Analysis of the urine by TLC (thin layer chromatography) and HPLC (high pressure liquid chromatography) indicated that 100% of the urinary radioactivity was found in polar metabolites of the initial compound, predominantly glucuronide and sulfate conjugates. Secretion was blocked by probenecid, the classical inhibitor of the organic anion transport system. Finally, it was shown that other organic anions including the herbicide, 2,4-D, were very effective inhibitors of the secretion of these PAH metabolites, suggesting that these 'less toxic' anions might potentiate PAH toxicity by prolonging their retention and promoting bioconcentration. (no Refs)

12. SPECIFICITY IN PEROXIDASE-CATALYZED ACTIVATION OF CARCINOGENS (MEETING ABSTRACT).

Wise R, Zenser TV, Davis BB
Departments of Biochemistry and Medicine Medical Center, Veterans Administration, St. Louis, MO, 63110
Proc Am Assoc Cancer Res; 23:316 1982

The hydroperoxidase component of prostaglandin endoperoxidase synthetase catalyzes the metabolic activation of kidney and bladder aromatic amine and 5-nitrofuran carcinogens. Direct mixed-function oxidase activation is not observed. In view of the wide distribution of heme peroxidases, the specificity of peroxidase-catalyzed activation was examined using 14C-benzidine and 2-amino-4-(5-nitro-2-furyl)-14C-thiazole (14C-ANFT) as substrates and prostaglandin hydroperoxidase (PG), horseradish peroxidase, lactoperoxidase and chloroperoxidase as enzymes. Binding of activated metabolites to protein was assessed following trichloroacetic acid precipitation and to transfer (t)-RNA following collection on glass fiber filters. All peroxidases studied activated 14C-benzidine to bind these macromolecules. By contrast, only PG hydroperoxidase catalyzed activation of 14C-ANFT. The rate of PG hydroperoxidase-catalyzed activation of 14C-ANFT was approximately one fourth that of 14C-benzidine. The rate of benzidine metabolism was 20.2 and 3.0 nmol/mg/min for protein and t-RNA binding, respectively. These results suggest that benzidine can be activated by a variety of heme peroxidases and probably functions as a hydrogen donor in these reactions. 5-Nitrofurans, such as ANFT, may be metabolized by a different mechanism. They may react with an oxidant released by PG hydroperoxidase. The only aerobic metabolism of ANFT thus far observed is that catalyzed by PG-hydroperoxidase. (no Refs)

MODIFICATION OF CARCINOGEN METABOLISM

13. METABOLISM OF (+-)-TRANS-7,8-DIHYDROXY-7,8-DIHYDRO-BENZO[A]PYRENE IN MOUSE LIVER MICROSOMES AND THE EFFECT OF 2(3)-TERT-BUTYL-4-HYDROXYANISOLE.

Dock L, Rahimtula A, Jernstrom B, Moldeus P
Dept. Forensic Medicine, Karolinska Institutet, Box 60400, S-104 01 Stockholm, Sweden
Carcinogenesis; 3(6):697-701 1982

The metabolism of (+-)-trans-7,8-dihydroxy-7,8-dihydrobenzo[a]pyrene (BP-7,8-diol) was examined using liver microsomes from mice maintained either on a standard laboratory food diet or on a mixture of ground food pellets and 2(3)-tert-butyl-4-hydroxyanisole (BHA, 7.5 g/kg food). Dietary BHA had a statistically significant inhibitory effect both on the formation of polar metabolites of BP-7,8-diol and on the covalent binding of reactive products to calf thymus DNA. When BHA (20 uM) was added in vitro to the microsomal incubation system, both the metabolism of BP-7,8-diol and the covalent binding of BP-7,8-diol metabolites to DNA, was reduced by approx 50% using either type of microsomes. The binding of [14C] 7beta,8alpha-dihydroxy-9alpha,10alpha-epoxy-7,8,9,10-tetrahydrobenzo[a]pyrene to calf thymus DNA was not affected by the presence of BHA. the reduced metabolism of BP-7,8-diol in microsomes from BHA-treated mice compared to control was not due to the effect of residual BHA in the microsomal preparation. These results show that BHA acts as a potent inhibitor of the activation of the proximate carcinogen BP-7,8-diol to reactive, DNA-binding products both when administered as a dietary constituent and as an additive to microsomal incubation systems. Both of these properties may be of relevance to the inhibitory effect of BHA on benzo[a]pyrene carcinogenesis. (Author abstract) (56 Refs)

14. EFFECT OF 2(3)-TERT-BUTYL-4-HYDROXYANISOLE ON BENZO[A]PYRENE METABOLISM AND DNA-BINDING OF BENZO[A]PYRENE METABOLITES IN ISOLATED MOUSE HEPATOCYTES.

Dock L, Cha YN, Jernstrom B, Moldeus P
Dept. Forensic Medicine, Karolinska Institutet, S-104 01 Stockholm, Sweden
Chem Biol Interact; 41(1):25-37 1982

Benzo[a]pyrene (BP) metabolism and the conjugation and DNA binding of BP metabolites, was studied using isolated hepatocytes from mice maintained on a diet containing 2(3)-tert-butyl-4-hydroxyanisole (BHA) (7.5 g/kg food) to discover the mechanisms involved in the anticarcinogenic effects of this antioxidant. The antioxidant feeding produced: (a) profound differences in the BP metabolite pattern, (b) no increase in the levels of either the glucuronic acid, the sulfate or the glutathione conjugates and (c) a marked decrease in the level of BP metabolites bound to intracellular DNA. Therefore, the inhibition of DNA-binding observed after administration of BHA, may be due to the change in BP metabolism rather than to an increase in the conjugation of reactive metabolites. (Author abstract) (39 Refs)

15. DIFFERENTIAL EFFECTS OF DIETARY AND INTRAPERITONEAL ADMINISTRATION OF ANTIOXIDANTS ON THE ACTIVITIES OF SEVERAL HEPATIC ENZYMES OF MICE.

Cha YN, Heine HS, Moldeus P

Dept. Pathobiology, Johns Hopkins Medical Institutions, Baltimore, MD

Drug Metab Dispos; 10(4):434-435 1982

Biochemical effects of ip administration 2(3)-tert-butyl-4-hydroxyanisole (BHA), 1,2 dihydro-6-ethyl-2,2,4-trimethylquinoline (EQ), and disulfiram (DSF) on female CD-1 mice were compared with those previously observed by dietary administration of the antioxidants. Dietary administration of BHA and EQ produced marked enlargement of the liver. In contrast, ip administration of the antioxidants for the same duration did not alter the liver weights. Pretreatment of mice with DSF, either in the diet or by ip injections, did not produce any changes in their liver weights. Feeding of BHA, EQ, and DSF all produced disproportionate increases in the activity of both flavin reductases. BHA produced a moderate increase of NADPH-cytochrome c reductase activity without any changes in cytochrome P450 levels. No effects on aminopyrine N-demethylation were noted but a marked increase of p-hydroxylation of aniline and a significant decrease of benzopyrene mono-oxidation occurred. Dietary EQ produced an increase in NADPH-cytochrome c reductase activity and marked elevation of cytochrome P450 levels. Concurrent with the increases, the rates of N-demethylation and of hydroxylation were greatly increased. However, the oxidation rate of benzopyrene was reduced. Changes produced by DSF were small if any. Differential effects produced on glucose 6-phosphate, glutathione reductase, and uridine diphosphate-glucose dehydrogenase are described. (17 Refs)

16. DOSE DEPENDENT INDUCTION OF RAT LIVER MICROSOMAL CYTOCHROME P-450 AND MICROSOMAL ENZYMATIC ACTIVITIES AFTER INHALATION OF TOLUENE AND DICHLOROMETHANE.

Toftgard R, Nilsen OG, Gustafsson JA

Dept. Pharmacology, Karolinska Institutet, Box 60400. S-104 01 Stockholm, Sweden

Acta Pharmacol Toxicol (Copenh); 51(2):108-114 1982

Sprague-Dawley rats were exposed, by inhalation, to toluene and dichloromethane (500, 1,500 or 3,000 ppm) and to benzene (1,500 ppm) for 3 days. Toluene and benzene increased the concentration of liver microsomal cytochrome P-450. A dose dependent increase in the in vitro liver microsomal formation of several metabolites of biphenyl and benzo(a)pyrene was observed for both dichloromethane and toluene. At the highest dose-level the increase in the in vitro formation of benzo(a)pyrene-7,8-dihydrodiol was more than three-fold for both dichloromethane and toluene whereas the formation of benzo(a)pyrene-4,5-dihydrodiol increased more than five-fold following exposure to toluene but less than two-fold after exposure to dichloromethane. Our results suggest that dichloromethane and toluene can modify the metabolism and thereby the toxicity of other environmental contaminants. (Author abstract) (30 Refs)

17. EFFECTS OF ESTRADIOL ON ENZYMES ASSOCIATED WITH BENZO(A)PYRENE METABOLISM (MEETING ABSTRACT).

Williams MT

Department of Biochemistry, University of South Florida, College of Medicine, Tampa, FL, 33612

Fed Proc; 41(3):1428 1982

Injection of female C57Bl/65 mice with estradiol (E2) 24 hours prior to, during and 24 hours after injection of 3-methylcholanthrene (3-MC) resulted in an apparent decrease in hepatic aryl hydrocarbon hydroxylase (AHH) activity when compared to AHH activity from animals receiving injection of 3-MC only. Moreover, AHH mediated binding of benzo(a)pyrene (BP) metabolites to DNA was inhibited between 35 and 45% in the 3-MC-E2 treated animals as compared to the 3-MC treated animals. The post-105,000 xg supernatant from E2 treated animals exhibitd significantly higher glutatione-S-transferase activity compared to supernatants from control animals. AHH activity in microsomes from control, E2 and 3-MC treated animals was significantly inhibited by BP quinones at a concentration as low as 2uM. AHH activity in microsomes from E2 treated animals was more sensitive to inhibiton by quinones than control AHH activity. Our data suggest that E2 may exert a direct inhibitory effect on hepatic AHH activity and also affect the activities of other enzymes associated with detoxification and inactivation of xenobiotics. (no Refs)

18. HORMONAL REGULATION OF PROCARCINOGEN BIOTRANSFORMATION (MEETING ABSTRACT).

Rapic V, Kanazir D

Boris Kidric Institute of Nuclear Sciences, Belgrade, Yugoslavia

Twelfth Annual Meeting of the European Environmental Mutagen Society, June 20-24, 1982, Dipoli, Espoo, Finland. European Environmental Mutagen Society 250 pp., 1982.

It is known that the activity of hepatic drug metabolizing enzymes depend on the hormonal status of experimental animals. In this work the effect of adrenalectomy and hydrocortisone treatment on hepatic microsomal activity in biotransformation of B(a)P (benzo(a)pyrene) and 2-AAF (acetylaminofluorene) in the Ames assay were examined. Male Wistar rats aged 2 months were bilaterally adrenalectomized and ip treated with hydrocortisone at a daily dose of 25mg/kg, for 4 days after operation. S9 fractions were used in Salmonella typhimurium assays. Cytochrome P-450 and aminopyrine N-demethylase were determined in microsomal fractions. The results of the Ames test show that adrenalectomy significantly decreases enzyme activity of S9 fraction in metabolic transformation of 2-AAF and B(a)P. The hormone treatment restores the enzyme activity but not to the level of control. The results on aminopyrine N-demethylase activity are similar to S9 activity. Adrenalectomy also lowers the cytochrome P-450 content, but administration of hydrocortisone does not restore it viably. (no Refs)

19. PROTECTIVE EFFECTS OF THE HERBICIDE TRIFLURALIN ON BENZO(A)PYRENE INDUCED PULMONARY ADENOCARCINOMA AND FORESTOMACH PAPILLOMAS IN FEMALE A/J MICE (MEETING ABSTRACT).

Triano EA, Lang WR, Kratky MT, Triolo AJ

Departments of Pharmacology and Pathology, Jefferson Medical College of Thomas Jefferson University, Philadelphia, PA, 19107

Fed Proc; 41(3):1548 1982

Mice were fed trifluralin (TF) at 1000, 1500, and 2000 ppm in the diet for 12 or 14 weeks. Tumors were induced by administering 3 mg of benzo(a)pyrene (BP) orally at two time periods. An inhibition of tumorigenesis in lung and forestomach by TF was observed when this herbicide was fed in the diet starting either one week before or one week following exposure to BP. Lung tumors were identified as bronchioloalveolar adenocarcinoma and forestomach tumors as squamous cell papillomas. BP is generally considered to be carcinogenic by virtue of its transformation by microsomal enzymes into chemically reactive intermediates which bind to critical macromolecules of target organs susceptible to tumors. Arylhydrocarbon hydroxylase (BP hydroxylase), a microsomal mixed-function oxygenase, was significantly increased in target (lung and forestomach) and in non-target (glandular stomach) organs when mice were fed TF for a duration of 14 weeks. No significant effects of TF were observed on hepatic enzyme activity. TF was found to decrease the binding of H3-BP to certain liver macromolecules. These findings suggest that various mechanisms resulting from TF treatment may be involved in the observed protection against BP-induced tumors. (no Refs)

20. ABERRATIONS OF THE HEME SYSTEM AND BENZO(A)PYRENE METABOLISM IN HEPATIC AND EXTRA-HEPATIC TISSUES OF STREPTOZOTOCIN-DIABETIC RATS (MEETING ABSTRACT).

Bitar M, Weiner M

University of Maryland School of Pharmacy, Baltimore, MD, 21201

Fed Proc; 41(3):1479 1982

Alterations in heme biosynthetic capability and benzo(a)pyrene (BP) hydroxylase activity were examined in hepatic and extra-hepatic tissues of streptozotocin (STZ)-diabetic Sprague-Dawley rats. Activities were measured 10, 30 and 90 days following the administration of STZ (65 mg/kg, iv). The basal levels of hepatic aminolevulinic acid synthetase (ALA-S) and aminolevulinic acid dehydratase were depressed approximately 50% in STZ-diabetic rats as compared to sham-operated animals. The activity of BP hydroxylase in liver microsomes of female diabetic rats was increased approximately 50% over controls, while a decrease was seen using the 9,000g supernatant fractions of adrenal tissue. In male STZ-diabetic rats, BP hydroxylase activity was decreased 25-60% in the liver, adrenal and testis. A further contrast was observed in the content of cytochrome P-450 in male and female diabetic rats, a decrease in the former and an increase in the latter. The rebound increase in ALA-S activity following the administration of cobalt to normal animals was not found in diabetic rats. Furthermore, the microsomal content of cytochrome P-450 and the activity of BP hydroxylase following cobalt administration were decreased to the same extent in both normal and diabetic rats. These data suggest that diabetes can significantly influence heme biosynthesis in the liver and xenobiotic metabolism in hepatic and extra-hepatic tissues. (no Refs)

21. METABOLIC CONVERSION OF GENOTOXIC CARCINOGENS BY UNTREATED AND AROCLOR-TREATED FIBROBLASTS (BHK21/C13) AND HEPATOMA CELLS (MH/CL) (MEETING ABSTRACT).

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Twelfth Annual Meeting of the European Environmental Mutagen Society, June 20-24, 1982, Dipoli, Espoo, Finland. European Environmental Mutagen Society 250 pp., 1982.

Cultured fibroblasts eg BHK21/C13 cells used in Styles, soft agar transformation assay, are known to be scarcely active in metabolizing xenobiotic chemicals, and are therefore coupled with mammalian S9 fractions for detecting procarcinogens. We have checked whether stimulation with Aroclor 1254 might result in an enhancement of metaboism in BHK21/C13 cells and, in parallel assays, in continuous-line MH1Cl epithelial cells, originated from the transplantable Morris 7795 rat hepatoma. The four carcinogens benzo(a)pyrene (BP), aflatoxin B1 (AFB1), 2-aminofluorene (2AF) and 4-nitroquinolino-N oxide (4NQO) were used as test compounds and his- strains of Salmonella typhimurium as indicators of their mutagenicity. No mutagenic metabolite of AFB1 was released from intact BHK21 or MH1Cl cell monolayers, whose growth medium had been supplemented either with DMSO (dimethyl sulfoxide) (controls) or Aroclor just after trypsinizaion. S9 fractions were prepared from rat liver of Sprague-Dawley rats, untreated (24 mg protein/ml) or Aroclor-treated (36 mg/ml); BHK21 cells, untreated (2.4 mg/ml) or treated with Aroclor-10 (2.2 mg/ml) or 1 ug/10(6) cells (2.9 mg/ml); MH1Cl cells, untreated (10.3 mg/ml) or treated with Aroclor-10 (9.6 mg/ml) or 1 ug/10(6) cells (9.9 mg/ml). Aroclor treatment was 48 hr at 37 C in serum-free medium of stationary-phase monolayers. These 8 S-9 fractions were mixed with co-factors and tested at equivalent protein concentration (300 ug/plate) in the Ames plate test (TA98 and TA100). The only significant effect produced by BHK21 fractions was slight reduction of 4NQO mutgenicity. Although less effective than liver fractions, MH1Cl fractions also activated 2AF, such an effect being potentiated by Aroclor stimulation. (no Refs)

22. ALTERATION OF BENZO[A]PYRENE HYDROXYLATION ACTIVITY WITH AGE IN HEPATIC AND EXTRAHEPATIC TISSUES (MEETING ABSTRACT).

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Fed Proc; 41(3):1564 1982

Benzo[a]pyrene (BaP) hydroxylation is catalyzed by microsomes from Sprague-Dawley rat liver, lung, kidney cortex and colon at varying rates at all age points examined including 2, 4, 10, 24 and 78 weeks. In liver BaP hydroxylation is low, but present at 2 weeks and peaks at 10 weeks and declines thereafter. A similar pattern is observed when BaP hydroxylation is induced with beta-naphthoflavone (beta NF) or phenobarbital (Pb). In the extrahepatic tissues BaP activity peaks at 4 to 10 weeks, but in contrast to liver, does not decline with age, but remains approximately at the peak level. Induction with Pb or beta NF is effective at all ages in colon and kidney cortex, but only beta NF induces activity in the lung. Cytochrome P-450 levels show a quite similar profile of changes with a few exceptions. There is an apparent increase in hepatic cytochrome P-450 content at 78 weeks which is not correlated with the observed decrease in BaP activity at 24 weeks. Lung cytochrome P-450 does not increase with Pb treatment, but does increase 3-fold over uninduced levels at 24 weeks with beta NF treatment. These results suggest a role for extrahepatic drug metabolism systems in metabolism of BaP. (no Refs)

23. HETEROGENEITY OF BENZO(A)PYRENE METABOLISM IN HUMAN AND RODENT CELL CULTURE (MEETING ABSTRACT).

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In Vitro; 18(3,part2):289 1982

Cell culture systems are now being routinely used to study the biochemical processing of carcinogens and mutagens. In addition, mammalian cell mutagenesis assays are using lawns of metabolically competent cells as activation systems to produce the reactive electrophile since the testor cells often do not possess the mixed function oxidases containing cytochrome P-450. We have compared benzo(a)pyrene metabolism in rat primary hepatocytes, liver epithelial cells and in normal and malignant human mammary cells. We have monitored the differences in the biochemical processing of the carcinogen in terms of organic-soluble derivatives, water-soluble conjugates and macromolecular binding. In addition, several rodent liver cells were tested as activation systems for the V-70 Chinese hamster cell mutagenesis assay. Significant differences in overall metabolism and pathway variance between human and rodent cells will be discussed. (no Refs)

24. DIFFERENCES IN METABOLISM OF CHEMICAL CARCINOGENS IN CULTURED HUMAN EPITHELIAL TISSUES AND CELLS.

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J Cell Biochem; 18(3):285-294 1982

Activation and deactivation of chemical procarcinogens were studied in cultured, nontumorous human epithelial tissues and cells. Procarcinogens were selected primarily on the basis that they represented several chemical classes and were found in the diet, drinking water, polluted air, and/or tobacco smoke. Conversion of the procarcinogens by cultured human tissues into metabolite(s) that bind covalently to DNA was investigated. Cultured human bronchus converted every procarcinogen studied into forms that bind to DNA. Carcinogens, such as aflatoxin B1, were activated to carcinogen-DNA adducts by cultured human tissues, bronchus, esophagus, colon, and bladder, even though epidemiological studies have not implicated aflatoxin B1 as a cause of cancer at these tissues. Metabolism of benzo[a]pyrene (BAP) and formation of DNA adducts were studied in cultured human tissues collected at the time of immediate autopsy. BAP metabolism and DNA binding were highest in the bronchus. Results indicated that quantitative extrapolations of carcinogen binding data may be possible among some, but not all tissues, and when different chemical classes of carcinogens are compared, quantitative and predictive correlations may frequently not be observed. Differences in carcinogen metabolism among people may be qualitative and/or quantitative. The magnitude of the differences ranges from 50-to 150-fold and is similar to that found in pharmacogenetic studies of drug metabolism. The rate-limiting enzymatic reaction could differ among humans and tissue types. (60 Refs)

25. CYTOCHROME P-450 AND PROSTAGLANDIN SYNTHETASE DEPENDENT METABOLISM OF (+/-)-BENZO(A)PYRENE-7,8-DIHYDRODIOL BY RAT ISOLATED PULMONARY CELLS (MEETING ABSTRACT).

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Fed Proc; 41(3):1571 1982

Exposure of lung to benzo(a)pyrene (BP) produces tumors presumably derived from clara and type II cells. The metabolism of (+/-) BP-7,8-dihydrodiol (BP-7,8-diol), was studied by both the cytochrome P-450 monooxygenase system and the prostaglandin synthetase system (PGS) using isolated rat type II and clara cells. These cells were prepared from control rats or animals pre-treated with beta-naphthoflavone. Clara and type II cells metabolized BP-7,8-diol in the presence of arachidonic acid (AA) or NADPH to 7,10/8,9 BP tetrol and 7/8,9,10 BP tetrol, the known solvolysis products of BP diol epoxide I. No detectable levels of tetrols were formed from BP diol epoxide II. The rate of metabolism of BP-7,8-diol in the type II cells by the AA dependent-system was about 2 fold higher than that of the NADPH system. The metabolism of BP-7,8-diol in clara cells by the NADPH dependent system was 2 fold higher than that of AA system. Pretreatment of animals with beta-naphthoflavone increased the metabolism of BP-7,8-diol 2 to 3 fold in clara and type II cells by both AA and NADPH dependent-systems. These results suggest that PGS and NADPH dependent metabolism vary widely between cells types. The relative contribution of these systems to chemical toxicity may depend on both the nature of the chemical and the target cell. (no Refs)

26. FORMATION OF DIHYDRODIOL METABOLITES OF BENZO(A)PYRENE IN CULTURED HUMAN AND MURINE SKIN CELLS.

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Anticancer Res; 2(1/2):89-94 1982

The formation of 7,8-and 9,10-dihydrodiol metabolites of benzo(a)pyrene (BP) was studied in cultures of human and murine origin focusing on the effect of aryl hydrocarbon hydroxylase inducers on the metabolite formation. Incubation of epithelial and fibroblastic cultures of human and murine origin resulted in the formation of two major radiolabeled compounds which were identified as trans-9,10-dihydrodiol-benzo(a)pyrene (9,10-DHDBP) and *trans*-7,8-dihydrodiol-benzo(a)pyrene (7,8-DHDBP). Autoradiographs of mouse epithelial and fibroblastic cell pretreated with and without benz(a)anthracene (BA) showed that both cell types are inducible to the formation of the metabolites. Pre-incubation with BA did not result in an increased metabolite formation. The induction ratio of each metabolite was calculated as the amount of metabolite/ug DNA formed in the BA-treated culture, divided by that in the control culture. The results for the various cultures and the in vivo experiments are summarized. Results showed that murine cultures exhibit inducible BP-metabolism towards 9,10-DHDBP and 7,8-DHDBP and none of the tested cultures of human cells are able to metabolize BP to a greater extent after pre-exposure to BA. (29 Refs)

27. A TWIN STUDY OF BENZO(A)PYRENE METABOLISM IN HUMAN HAIR FOLLICLES (MEETING ABSTRACT).

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Twelfth Annual Meeting of the European Environmental Mutagen Society, June 20-24, 1982, Dipoli, Espoo, Finland. European Environmental Mutagen Society 250 pp., 1982.

Aryl hydrocarbon hydroxylase (AHH) has been considered as a key enzyme in the metabolism of polycyclic aromatic hydrocarbons to biologically active intermediates. Earlier twin studies have suggested that AHH-inducibility is under genetic control using lymphocytes as biopsy-tissue. However, the use of lymphocytes for studies on carcinogen metabolizing enzymes has been criticized for various reasons. We have used human hair follicles, an easily obtainable source of epithelium, to study basal levels of benzo(a)pyrene (BP) metabolism in monozygotic twins (MZ), dizygotic twins (DZ) and pairs of unrelated individuals. Attention was focused on the formation of the 7,8-and 9,10-dihydrodiol metabolites of BP, the direct precursors of the ultimate carcinogens, the diol epoxides. It was found that the intratwin differences for MZ are less than for DZ while DZ exhibit smaller differences than pairs of unrelated individuals. (2 Refs)

28. ARYL HYDROCARBON HYDROXYLASE OF RAT BRAIN MITOCHONDRIA: PROPERTIES OF AND EFFECT OF INHIBITORS AND INDUCERS ON, ENZYME ACTIVITY.

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Arch Biochem Biophys; 217(1):205-215 1982

The characterization and properties of aryl hydrocarbon hydroxylase were studied in mitochondria and microsomes of rats, guinea pigs and mice. AHH required oxygen and NADH for optimum activity. NADH-dependent mitochondrial (mt)AHH followed the order: mice equal to or greater than guinea pig greater than rat, while that of NADPH supported mtAHH was: rat greater than guinea pig equal to or greater than mice. Specific activity of NADH-dependent mtAHH was similar in various regions of brain except for high activity in the olfactory lobes. The Km of NADH-dependent mtAHH was 1.18 uM with benzo(a)pyrene (BP) as a substrate, which was 5-6x lower than that in rat brain, 6.66 uM. NADH-dependent mtAHH was inhibited by KCN in a concentration-dependent manner while NADPH-supported mtAHH was insensitive to cyanide. Both brain microsomal NADH and NADPH supported AHH were inhibited by KCN in a concentration-dependent manner. Carbon monoxide inhibited NADH-dependent mtAHH but was without effect on NADPH-dependent mtAHH. Both mitochondrial NADH and NADPH-dependent AHH activities were induced by 3-methylcholanthrene (MC; 64-73%) and BP (91-92%) pretreatments while none occurred with phenobarbital. Both basal and MC-induced NADH-dependent mtAHH activity were inhibited by 1-benzylimidazole, SKF 525 A, metyrapone, and alpha-naphthoflavone. In rats, NADH-dependent mtAHH activity increased gradually with onset of development and attained a steady state after 49-56 days of age. Specific enzyme activity increased eight- to ninefold between 7-and 56-day-old rats. (47 Refs)

29. CHEMICAL CARCINOGEN ACTIVATION IN THE RAT MAMMARY GLAND: INTRAORGAN CELL SPECIFICITY.

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Carcinogenesis; 3(6):667-669 1982

Cells from 50-55 day old virgin Sprague-Dawley female rat mammary gland were divided into parenchymal (epithelial) and stromal enriched populations. The ability of these cells to activate carcinogens was quantitated employing a mediated mutagenesis assay. In addition, the populations' ability to produce water soluble metabolites from these carcinogens was estimated. We report that the potent mammary carcinogen 7,12-dimethylbenz[a]anthracene was activated by both mammary parenchymal and stromal cells, while the non-mammary carcinogen aflatoxin B1 was not activated by either cell type. However, the weak mammary carcinogen benzo[a]pyrene was activated by the stromal cells and not by the parenchymal cells from which mammary carcinomas arise. The data suggest that the intra-organ relationship between cell types that activate a carcinogen, and cell types that undergo neoplastic transformation, may in part help explain the organ specific potency of a carcinogen. (Author abstract) (7 Refs)

30. DIFFERENTIAL EFFECTS OF RETINOIC ACID AND 7,8-BENZOFLAVONE ON THE INDUCTION OF MOUSE SKIN TUMORS BY THE COMPLETE CARCINOGENESIS PROCESS AND BY THE INITIATION-PROMOTION REGIMEN.

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Cancer Res; 42(9):3519-3525 1982

The present study was designed to elucidate differences in the mechanism of the induction of mouse skin tumors either by the initiation-promotion regimen or by the complete carcinogenesis process. The protocols used to elicit skin tumors were: (a) by the initiation-promotion regimen, a single application of 0.2 umol of 7,12-dimethylbenz[a]anthracene (DMBA) followed by twice-weekly applications of 12-O-tetradecanoylphorbol-13-acetate (TPA); and (b) by the complete carcinogenesis process, a single application of 3.2 umol of DMBA without TPA treatment, or 0.2 umol of DMBA applied once weekly, or 1, 10, 50, or 100 umol of DMBA applied twice weekly without application of TPA. The biology of tumor formation by the initiation of tumors with a single application of 0.2 umol DMBA followed by twice-weekly applications of TPA differs from tumor induction by once-weekly 0.2-umol doses of DMBA. In the latter case, papillomas developed more slowly and were less common (the tumor induction time was long; tumor yield was less), but carcinomas appeared much earlier. Retinoic acid, a potent inhibitor of tumor promotion by TPA, failed to inhibit and under some experimental conditions significantly (p less than 0.001) enhanced tumor formation by DMBA. Also retinoic acid did not inhibit ornithine decarboxylase induction by DMBA. In contrast, 7,8-benzoflavone, which did not inhibit the induction of ornithine decarboxylase activity by TPA, inhibited the induction of ornithine decarboxylase activity and tumor formation by DMBA. The results indicate that the nature and the mechanism of the biochemical events elicited by the presumed promoting component of carcinogenesis by a complete carcinogen are different from those of the tumor promoter TPA. (Author abstract) (21 Refs)

31. LACTATIONAL INDUCTION OF HYDROXYLATION OF CARCINOGENS IN SUCKLING RATS BY INDUCERS OF CYTOCHROME P1-450 (MEETING ABSTRACT).

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Fed Proc; 41(3):1425 1982

Modification of carcinogen metabolism in suckling young (SY) through lactational transmittal of pharmacologically active compounds is of considerable interest. We have examined the effects of ip injections to lactating rats (LR) of 3-methylcholanthrene (3-MC) or beta-naphthoflavone (beta-NF) (40 mg/kg of b wt in corn oil for 3 days) on enzyme activities of hepatic microsomes (HM) of their SY. The levels of cytochromes P-450 (P1-450) and bs and activities of NADH- and NADPH-cytochrome c reductases were similar to those of HM of SY from corn oil-treated LR. The apparent induction of cytochrome P1-450 in HM of SY of 3-MC- or beta-NF-treated LR was shown by the increased hydroxylations of benzo[a]pyrene (B[a]P) and N-2-fluorenylacetamide (2-FAA). In the presence of 0.1 mM alpha-NF (alpha-naphthoflavone), the levels of hydroxylation of B[a]P or 2-FAA were similar in all 3 sets of SY and were 2.7-or 5.0-fold greater, respectively, than their basal levels. This suggests that although alpha-NF in vitro stimulates the basal hydroxylating enzyme activities, it inhibits the cytochrome P1-450-induced activities as it does in HM of LR. In the latter, alpha-NF was a more potent inhibitor than beta-NF. Binding to HM showed that beta-NF (type I) binds with a higher affinity than the type I substrates B[a]P and 2-FAA, whereas alpha-NF gives a qualitatively different binding spectrum suggestive of multiple binding sites. (no Refs)

32. EFFECTS OF SELENIUM ON MOUSE MAMMARY TUMORIGENESIS AND GLUTATHIONE PEROXIDASE ACTIVITY.

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Anticancer Res, 1(6):377-382 1981

Effects of selenium (SeO2, and Na2SeO3) were examined on the tumor-producing capabilities of CV-7 line, 7,12-dimethylbenz(a)anthracene (DMBA)-induced mammary tumorigenesis in BALB/c female mice, and mammary glands of mice which had been hormonally stimulated prior to DMBA treatment. Selenite supplementation reduced the incidence of CV-7 mammary tumors from 70% (21/30) to 20% (6/30) over a period of 38 wk. Further appearance of tumors in the selenite-treated mice was markedly delayed. Samples of normal mammary gland and preneoplastic nodule outgrowth tissues were removed for glutathione-peroxidase (GSH-Px) activity 22 wk after transplantation when the mammary tumor incidences in the control and selenite-treated mice were 47 and 7%, respectively. Preneoplastic tissue had twice the amount of GSH-Px activity than normal mammary gland in both normal and selenite-treated groups. No indication was observed that the expression of murine mammary tumor virus proteins in the preneoplastic tissues were qualitatively different in selenite-treated mice. Selenite at 7 and 10.5 ppm reduced the incidence of DMBA-induced mammary tumors from 55% to 5 and 10%, respectively. In hormone pretreated mice, DMBA-induced tumors arose over a period of 54 wk after carcinogen treatment. Selenite reduced the incidence of mammary tumors from 37 to 14%. Results demonstrated that selenium, in the form of inorganic selenite, is a potent chemoprotective agent for both viral and chemical carcinogen-induced mouse mammary tumorigenesis. (35 Refs)

33. MUTAGENICITY OF N-NITROSOPYRROLIDINE: INFLUENCE OF THE METHOD AND EFFECT OF PHENOBARBITAL AND COBALTOUS CHLORIDE PRETREATMENT (MEETING ABSTRACT).

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Twelfth Annual Meeting of the European Environmental Mutagen Society, June 20-24, 1982, Dipoli, Espoo, Finland. European Environmental Mutagen Society 250 pp., 1982.

It has been shown that the mutagenicity of N-Nitrosopyrrolidine (NPyrr) was related to its metabolism. Using the plate incorporation test, the mutagenic activity of of NPyrr towards Salmonella Typhimurium TA 1530 was similar to that previously reported: the microsomal friction was less effective than the postmitochondrial supernatant; the cystosol was ineffective; the activity of the combination of microsomes and cytosol was identical to that of postmitochondrial supernatant. Pretreatment of rats by phenobarbital remained without effect. The mutation rates observed during 2 hours incubation in liquid medium at 37 C were different from these detected in the plate incorporation test. In this method, the mutagenic activity observed in the presence of microsomal fraction was similar to that detected with postmitochondrial supernatant. Moreover, phenobarbital pretreatment, an inducer of cytochrome P mixed function oxidases system, increased the mutation rate; pretreatment with cobaltous chloride, an inhibitor of the in vivo synthesis of cytochrome P450 decreased the mutation rate. (no Refs)

34. INHIBITION OF DIMETHYLNITROSAMINE METABOLISM BY SOME HETEROCYCLIC COMPOUNDS AND BY SUBSTRATES AND INHIBITORS OF MONOAMINE OXIDASE IN THE RAT.

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Cancer Res; 42(9):3761-3765 1982

Pretreatment of rats with a number of nitrogen-containing heterocyclic compounds was found to inhibit markedly the metabolism of dimethylnitrosamine (DMN) in terms of both CO2 excretion and decline in blood DMN concentration. However, many of these compounds had either much less or no inhibitory effect on the in vivo metabolism to CO2 of a typical mixed-function oxidase substrate, aminopyrine. In addition, a number of model inhibitors of monoamine oxidase (MAO) activity also inhibited DMN metabolism in the intact animal, and a number of primary amines, known substrates of hepatic MAO, inhibited DMN metabolism but not that of aminopyrine in the isolated perfused liver system. These results, together in vitro data and previously reported studies on the effect of MAO inhibitors and substrates on the mutagenicity of DMN, suggest that the metabolism and bioactivation of DMN may be in part mediated by a MAO type of enzyme activity. (Author abstract) (46 Refs)

35. IN VIVO PROTECTION BY INDOLE-3-CARBINOL AGAINST CARCINOGEN COVALENT BINDING TO MOUSE HEPATIC MACROMOLECULES (MEETING ABSTRACT).

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Fed Proc; 41(3):1599 1982

Indole-3-carbinol (I3C) is a normal constituent of the human diet and is contained in such cruciferous vegetables as cabbage, broccoli, brussels sprouts and cauliflower. When ingested by rodents, this compound has been shown to induce aryl hydrocarbon hydroxylase activity and to confer some protection against polynuclear aromatic hydrocarbon induced neoplasia. We examined the pattern of microsomal enzyme induction in mice gavaged with I3C in corn oil. Hepatic cytochrome P-450, aryl hydrocarbon hydroxylase, and ethoxyresorufin deethylase reached maximum levels in about 5 days. These and other data suggest that the form of cytochrome P-450 induced by I3C is similar to that produced by aryl hydrocarbons. When mice were gavaged with I3C followed by gavage with 14C-N-nitrosodimethylamine (NDMA) or 14C benzo(a)pyrene (BaP), there resulted a large decrease in the total amount of radioactivity covalently bound to hepatic macromolecules, when compared with corn oil gavaged controls. This decrease in covalent binding was evident in nuclear, mitochondrial, microsomal and supernatant subcellular fractions, as well as in DNA, RNA and protein in each subcellular fraction where they occur. The decrease in binding of NDMA and BaP metabolites occurred within 1 hr after I3C administration and therefore appeared to have no relationship to the microsomal enzyme induction discussed above. (no Refs)

36. EFFECT OF DIETARY FAT TYPE ON THE TOXICITY, METABOLISM AND MUTAGENICITY OF N-NITROSODIMETHYLAMINE IN MICE (MEETING ABSTRACT).

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Fed Proc; 41(3):1548 1982

The influence of dietary fat on toxicity, metabolism and mutagenicity of N-nitrosodimethylamine (DMN) was studied in male Swiss Webster mice. Mice fed fat free, tallow (10%), corn oil (10%) and lab chow diets for four weeks were injected with 7 mg/kg, ip of DMN followed by a regimen of 10 PPM in drinking water 5 days/week for 4 weeks. Treatment with DMN decreased serum protein levels and body weights in all mice while significantly increasing serum alkaline phosphatase and glutamic-oxaloacetate transaminase only in corn oil dieted mice. Pathological examination showed no abnormalities in control animals while DMN treatment produced diet related vascular lesions in the central veins and mild ascites due to hypoproteinemia. The catalytic coefficients (Vmax/Km (diet treated)/Vmax/Km FF diet) for demethylase I of post mitochondrial fraction (S-9) of livers from mice fed tallow, corn oil and lab chow diets were increased, while the catalytic coefficients for Demethylase II were decreased in all animals when compared to those fed fat-free diet. DMN treatment reduced the metabolism of DMN which was reflected in a decrease in mutagen formation by S-9 fractions. (no Refs)

37. DOLICHOL CONTENT AND REGULATION DURING RAPID GROWTH AND CARCINOGENESIS (MEETING ABSTRACT).

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Fed Proc; 41(3):666 1982

Rat liver dolichol contains mostly 18 and 19 isoprene residues, over 90% of which is in the non-phosphorylated form. The lipid is synthesized by a series of condensation reactions, and preferential labeling of short chain polyprenols can be obtained after in vivo labeling with mevalonate-3H. Dolichol content is low in the liver of newborn rats and is greatly increased during liver regeneration. Administration of N-nitrosodiethylamine to rats more than doubles the dolichol content, whereas protein glycosylation is decreased. The dolichol content is increased in preneoplastic noduli of the liver. The concentration in the microsomes of the noduli was ten times above that in the control microsomes. The dolichol pattern exhibits relatively small variations in contrast to the primary hepatocellular cancer in human liver where dolichols with shorter chain length dominate. The concentration of dolichol phosphate decreases, but this is not due to decreased synthesis of the polyprenol. The CTP (cytidine triphosphate)-mediated phosphorylation of both dolichol (C55) and dolichol (C100) are lowered and, at the same time, dolichol monophosphatase is increased. There is also an increase in glucosaminidase activity. As a consequence, there is some decrease in protein glycosylation. The experiments suggest a regulatory role of dolichol in oligosaccharide biosynthesis during chemical carcinogenesis. (no Refs)

38. DIETARY PROTEIN CONCENTRATION AND THE METABOLISM OF 1,2-DIMETHYLHYDRAZINE BY MICE.

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Diss Abstr Int [B]; 42(9):3636-B 1982

At concentrations ranging from 2.5 to 10 mM, 1,2-dimethylhydrazine (DMH) and azoxymethane (AOM) did not increase the mutation frequency of Salmonella typhimurium (Strain G-46) in vitro. Murine liver microsomes and cofactors caused a 40-fold increase in mutation frequency with dimethylnitrosamine (DMN) but not with DMH or AOM in vitro. Methylazoxymethanol (MAM) was mutagenic in vitro without activation by liver preparations. The conversion of DMH, AOM, and MAM to mutagens was studied in growing male B6C3F1 mice fed isocaloric, semipurified casein, sucrose:dextrin diets containing 2.5, 5, 10, 20, or 40% protein. Mutagen formation from DMH and MAM varied slightly with diet but from AOM was directly proportional to dietary protein concentration. The percent of [14C]-DMH expired as a promutagen by growing mice fed 2.5, 10, or 40% protein was 63 +/-4, 44 +/-3, and 38 +/-3. The metabolism of DMH to mutagenic endproducts by mice was rate-limited by the conversion of azomethane to AOM and at least partially carried out by the liver. Increasing protein intake increased the bioactivation of DMH. AOM, and MAM and 2.5% protein diets caused greater expiration of promutagens from DMH, thereby decreasing the body burden of retained carcinogen. (no Refs)

39. DIETARY OROTIC ACID, A NEW SELECTIVE GROWTH STIMULUS FOR CARCINOGEN ALTERED HEPATOCYTES IN RAT.

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Cancer Lett; 16(2):191-196 1982

A new dietary protocol is described wherein feeding a diet containing orotic acid (OA), a precursor of pyrimidine nucleotide biosynthesis, selectively stimulates the growth of 1,2-dimethylhydrazine (DMH) modified cells to form gamma-glutamyltransferase positive hepatocytes in Fisher F344 rats. Experimental protocol is presented in detail. Following the 'initiating' treatment with DMH, six foci/square cm (cm2) were obtained in the liver of rats fed 1% OA diet compared to one or two foci/cm2 observed in the liver of rats fed a control diet. Prolonging the OA diet to 10 wk resulted in an increase in the number of foci up to 14/cm2. When feeding OA was coupled with administration of a single necrogenic dose of CCl4, the number of foci generated increased from 6-24 in 5 wk, and from 14-39 in 10 wk. Administration of CCl4 even in the absence of OA resulted in an increase in the number of foci. Results suggested that not only the carcinogen-altered hepatocytes differ from the normal in the response to an exogenous liver cell proliferation stimulus, but also that OA further modifies the carcinogen-altered cells in such a way that they respond to an even greater extent to the liver cell proliferative stimulus. (19 Refs)

40. EFFECT OF DIET ON THE METABOLISM OF 1,2 DIMETHYLHYDRAZINE (DMH) IN THE RAT (MEETING ABSTRACT).

Clauert HP, Bennink MR
Michigan State University, East Lansing, MI, 48824

Fed Proc; 41(3):356 1982

Dietary fat and liver have been shown to influence DMH-induced colon carcinogenesis in experimental animals. One possible mechanism is that diet alters DMH metabolism. In this experiment, we examined the effect of dietary fat, wheat bran, and agar on 1) the metabolism of DMH to products which bind to DNA in rat colon epithelial cells (CEC), and 2) the clearance of DMH and its metabolites from blood. Diets were fed for four weeks; labeled DMH was then injected ip and rats were killed at various time intervals (12-96 hours). CEC were isolated from the colon and DNA was purified from CEC. Maximum binding DMH metabolites to DNA was seen 36 hours after the injection of DMH. The amount of 14C binding to DNA was not altered by diet but a diurnal variation was evident. Maximum 14C binding at 9 pm was 32-109% greater than 14C binding at 9 am. Serum radioactivity was greater in rats fed the high-fat diet and lower in rats fed the wheat bran compared to the control group. 14C disappearance from serum fit a 'two-pool model' with half-life for the first pool ranging from 27 to 33 hr and half-life for the first pool ranging from 62 to 71 hr; diet did not alter half-life for either pool. This experiment shows that diet does not alter the amount of DMH metabolites bound to DNA in CEC even though diet does change the level of DMH plus its metabolites in serum. It appears that there is a marked diurnal variation in DMH metabolism. (no Refs)

41. INHIBITION OF AFLATOXIN B1 CARCINOGENESIS IN RAINBOW TROUT BY DIETARY BETA-NAPHTHOFLAVONE (BETA-NF), AND INDOLE-3-CARBINOL (I-3-C) (MEETING ABSTRACT).

Hendricks JD, Nixon JE, Bailey GS, Sinnhuber RO
Department of Food Science and Technology, Oregon State University, Corvallis, OR, 97331

Toxicologist; 2(1):102 1982

Several compounds such as flavonoids, selenium, antioxidants and certain vitamins reportedly reduce the induction of cancer in experimental animals, and many function by affecting the mixed-function oxidase (MFO) system. The following compounds: 50 and 500 ppm beta-NF, 1000 ppm flavone, 1000 ppm of a tangeretin-nobilitin mixture, 1000 ppm beta-ionone, 1000 ppm I-3-C and 2000 ppm quercetin were examined for protection against aflatoxin B1 (AFB1) hepatocarcinogenesis and induction of the MFO system in rainbow trout. These compounds were fed to fingerling rainbow trout for 2 months. At that time the activity of several MFO enzymes and cytochrome P450 content were measured and the trout were exposed to 20 ppb AFB1 for 10 days in the same diets. After feeding the test diets without AFB1 for another month and basal diet for 11 months, the tumor incidence was determined. Beta-NF induced the trout MFO system in a dose-dependent manner while tangeretin-nobilitin was less effective. Flavone, quercetin, beta-ionone and I-3-C did not induce the MFO system. I-3-C and beta-NF provided marked protection against AFB1-induced hepatocarcinogenesis, while the other compounds were ineffective. Tumor incidences were 5.1% for 1000 ppm I-3-C, 7.5% for 500 ppm beta-NF and 19.6% for 50 ppm beta-NF, compared to 44.9% for the AFB1-positive control. (no Refs)

42. EFFECT OF INCREASING LEVELS OF DIETARY PROTEIN ON THE METABOLIC ACTIVATION AND COVALENT BINDING OF AFLATOXIN B1 (MEETING ABSTRACT).

Hayes JR, McCall CO, Bagley DM
Department of Pharmacology Medical College of Virginia, Virginia Commonwealth University, Richmond, VA

Toxicologist: 2(1):25 1982

Low dietary protein levels (5%) decrease the hepatocarcinogenicity of aflatoxin B1 (AFB1), in part due to decrease in hepatic microsomal mixed function oxidase (MFO) activity, which activates AFB1 to its ultimate carcinogen. Although low levels of dietary protein are consumed by certain populations, others may consume protein above that required for maintenance. This study was designed to ascertain the effects of increasing levels of dietary protein on the metabolic activation of AFB1. Male, weanling Sprague-Dawley derived rats fed the AIN-76 semi-purified diet with casein levels of 5, 10, 20, 30 and 40% for 10 days. Body weight increased until protein levels reached 20% and then became asymptotic. Liver weights were higher only in the 5 and 10% groups due to lipid infiltration. Microsomal protein increased with dietary protein up to 20% and then became asymptotic. N-demethylation of ethyl-morphine (EM) increased until dietary protein levels reached 30% and then became constant. Cytochrome c reductase activity and cytochrome P-450 levels followed a trend identical to EM metabolism. In vitro metabolic activation of AFB1 to a produce(s) capable of covalently binding DNA increased until a level of 30% protein was reached and then became asymptotic. In vivo covalent binding of an AFB1 metabolite(s) to hepatic DNA, RNA and protein followed the same trend as the in vitro studies. Inappropriately low levels of dietary protein may be protective in respect to AFB1 carcinogenicity, but high levels may increase risk. (no Refs)

43. THE RELATIONSHIP BETWEEN AGING AND CANCER: AGE-RELATED CHANGES IN THE ABILITY OF THE LIVER TO METABOLIZE AFLATOXIN B1 (MEETING ABSTRACT).

Richardson A
Department of Chemistry, Illinois State University, Normal, IL, 61761
16th Annual Meeting of the Great Lakes ACS Region, June 7-9, 1982, Normal, Illinois. American Chemical Society 101 pp., 1982.

Although the incidence of cancer increased dramatically with increasing age, the exact relationship between aging and cancer is not clearly understood. It is possible that changes in biochemical reactions, which arise from the aging process, may play a role in the development of cancer induced by chemical carcinogens. However, results from research in the area of aging and cancer are contradictory. Previous investigators have used a holistic approach to studying the relationship between aging and cancer. Therefore, we focused on the effect of aging on the metabolism of the chemical-procarcinogen, aflatoxin B1 (AFB1) by liver extracts (S-9 and microsomes) from 4-to 27-month old male Fischer F344 rats. The Ames Salmonella Bioassay was used to quantify the activation of AFB1. The number of revertants produced by the S-9 or microsomes decreased 40 to 50% between 12 and 27 months of age. The formation of AFB1-DNA adducts by the S-9 fraction also decreased with increasing age. The metabolism of AFB1 to chloroform-soluble, water-soluble, and alcohol-insoluble metabolites also decreased as a function of age. Except for aflatoxicol, the formation of all chloroform-soluble metabolites of AFB1 decreased between 12 and 27 months of age. However, the formation of aflatoxicol increased slightly with age. The age-related decrease in AFB1 metabolism was correlated to a decrease in the mixed function monooxygenase system and could potentially result in an increase in the vulnerability of an organism to the carcinogenic effects of AFB1. (no Refs)

44. EFFECT OF AGE ON THE ABILITY OF RAT LIVER TO METABOLIZE THE CHEMICAL CARCINOGEN AFLATOXIN B1.

Jayaraj AA
Illinois State University, Normal, IL
Diss Abstr Int [B]; 42(10):4046-B 1982

The ability of liver fractions from 4-to 30-month-old Fischer F344 rats to activate and metabolize aflatoxin B1 (AFB1) in vitro was studied. The activation of AFB1 was measured by the Salmonella/microsome test and by its ability to bind to DNA in vitro. The metabolism of AFB1 was determined by measuring the conversion of AFB1 to water-soluble and CHCl(3)-soluble metabolites. The activation of AFB1 to compounds that are mutagenic in the Samonella/microsome test and to compounds that bind to DNA in vitro by liver S-9 and microsomes from male Fischer F344 rats decreased approximately 50% with increasing age. The in vitro metabolism of AFB1 by liver S-9 and microsomal fractions decreased significantly with increasing age. The metabolism of AFB1 to water-soluble and CHCl(3)-soluble metabolites was lower for liver preparations from 26-month-old than for 4 and 12-month-old male rats. The proportion of aflatoxicol produced by liver S-9 from male Fischer F344 rats increased approximately two-fold between 4 and 26 months of age. This increase could potentially increase the sensitivity of the organism to AFB1-induced hepatocarcinogenesis. Liver microsomal cytochrome P450 decreased approximately 50% between 4 and 26 months of age. A 60% decrease in the benzopyrene hydroxylase and benzphetamine demethylase activities was observed between 4 and 26 months of age. No age-related change in the ability of S-9 fractions from the liver of female Fischer F344 rats to activate AFB1, to its metabolites that are mutagenic in the Salmonella/microsome test was observed. (no Refs)

45. ACYL GROUP COMPOSITION OF TISSUES OF RATS FED 13-CIS-RETINOIC ACID (MEETING ABSTRACT).

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Department of Biochemistry, Louisiana State University Medical Center, New Orleans, LA, 70119
Fed Proc; 41(3):357 1982

It is known that 13-cis retinoic acid has been used to prevent tumors induced in different tissues by chemical carcinogens. Its effect on lipid composition and metabolism of tissues are not known. The purpose of the present investigation was to determine if 13-cis retinoic acid would also induce changes in fatty acid composition of tissue lipids. Three groups of male, weanling, Sprague-Dawley rats were fed diets containing 0, 100 or 300 mg of 13-cis retinoic acid per Kg diet. Rats were killed four weeks after initiating the dietary regimes. Plasma, liver, lung, heart and kidneys were extracted for total lipids and the fatty acid composition was determined. The results show that the proportions of 16:1, 18:1, 18:2 and 20:3 omega 6 were higher whereas those of 20:4 were lower in total lipids of plasma and liver of rats fed 13-cis retinoic acid as compared with the controls. There were no significant differences in the fatty acid patterns of other tissues. The results suggest that retinoic acid can alter the fatty acid composition of tissues, but this effect is selective depending upon the nature of the tissue. This selective effect of 13-cis retinoic acid on fatty acid composition of tissues may possibly be exerted via microsomal desaturases and chain elongases. (no Refs)

46. THE EFFECT OF PH CHANGES OF WATER ON THE HEPATIC METABOLISM OF XENOBIOTICS IN FISH.

Laitinen M, Nieminen M, Hietanen E
Dept. Physiology, Univ. Kuopio, P.O. Box 138, SF-70101 Kuopio, Finland
Acta Pharmacol Toxicol (Copenh); 51(1):24-29 1982

In order to determine the effect of pH changes of water or the metabolism of xenobiotics, fish were exposed for 8 hr to the acidic water (pH3). Two fish species were used, lavaret, (Coregonus lavaretus), and splake (Salvelinus fontinalis X Salvelinus namaycush). The metabolism of xenobiotics was monitored by analyzing aryl hydrocarbon hydroxylase, epoxide hydrase and ethoxycoumarin O-deethylase activities as well as the activity of UDP-glucuronosyltransferase using both p-nitrophenol and 4-methylumbelliferone as aglycones. A difference was found between species in measured basal activities. The aryl hydrocarbon hydroxylase activity, epoxide hydrase activity and ethoxycoumarin O-deethylase activity were higher in the splake than in the lavaret. No clearcut differences were de tected in UDPglucuronosyltransferase activities. When fish were exposed to water at pH 3, the aryl hydrocarbon hydroxy lase activity and epoxide hydrase activity in the splake were lower than in the control fish. The ethoxycoumarin O-deethy lase activity was higher in the lavarets at pH 3 than in the con trols. The UDPglucuronosyltransferase activity was higher i both splakes and lavarets exposed to pH 3 when analyzed afte trypsin digestion of microsomes and with 4-methylumbellifer one as an aglycone. (Author abstract) (18 Refs)

MUTAGENICITY OF ACTIVATED METABOLITES OF CARCINOGENS

47. FORMATION OF MUTAGENIC METABOLITES FROM BENZO(ALPHA)PYRENE AND 2-AMINOANTHRACENE BY THE S-9 FRACTION FROM THE LIVER OF THE NORTHERN PIKE (ESOX LUCIUS): INDUCIBILITY WITH 3-METHYLCHOLANTHRENE AND CORRELATION WITH BENZO[ALPHA]PYRENE MONOOXYGENASE ACTIVITY.

Balk L, Depierre JW, Sundvall A, Rannug U
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Chem Biol Interact; 41(1):1-13 1982

The mutagenicity of benzo[a]pyrene and 2-aminoanthracene in the Ames test using the S-9 fraction from the liver of the Northern pike (Esox lucius) was tested. S-9 fractions were prepared both from fish injected intraperitoneally with 3-methylcholanthrene and from control animals. In addition benzo[a]pyrene monooxygenase activity was assayed in the same S-9 fractions used in the Ames test. S-9 fractions from the liver of the Northern pike were found to convert benzo[a]pyrene and 2-aminoanthracene to mutagenic metabolites. The number of revertants obtained was increased 2-4-fold in the case of 2-aminoanthracene and 3-14-fold in the case of benzo[a]pyrene by pretreatment of the pike with a single intraperitoneal injection of 3-methylcholanthrene. This injection also caused a two- to six-fold increase in the benzo[a]pyrene monooxygenase activity of the S-9 fractions used. These increases in mutagenicity and activity occur mainly during the first 4-12 days after the injection, but further small increases are observed for as long as 60 days. A strong positive correlation was found between the benzo[a]pyrene monooxygenase activity of the S-9 fractions used and their ability to give rise to revertants in the Ames test using 2-aminoanthracene or benzo[a]pyrene. This indicates that the major determining factor in the production of reactive metabolites which attack DNA in this in vitro system is the activity of the Phase I cytochrome P-450 system. (Author abstract) (26 Refs)

48. MUTAGENICITY OF BENZO[A]PYRENE AND THE ANTIOXIDANT PHENOL AT THE HGPRT LOCUS OF V79 CHINESE HAMSTER CELLS.

Paschin YV, Bahitova LM
Inst. Genetics, Acad. Sciences, USSR, Moscow 117809, USSR
Mutat Res; 104(6):389-393 1982

The mutagenicity of benzo(a)pyrene (BP, up to 25 ug/ml) and phenol (PHE; up to 500 ug/ml) towards the hypoxanthine guanine phosphoribosyl transferase (HGPRT) locus of V79 Chinese hamster cells was investigated. Both BP and PHE increased the frequency of azaguanine-resistant mutants over the spontaneous level. While PHE alone had no effect on cell survival, BP plus PHE decreased the viability of wild-type V79 cells to 1% after treatment with metabolic activating mixture. (6 Refs)

49. A SENSITIVE FLUOROMETRIC ASSAY FOR EPOXIDE HYDRATASE.

Hukkelhoven MW, Vromans EW, Vermorken AJ, Bloemendal H
Res. Unit for Cellular Differentiation and Transformation, Univ. Nijmegen, 6525 EZ Nijmegen, The Netherlands
FEBS Lett; 144(1):104-108 1982

A rapid and very sensitive fluorometric assay for epoxide hydratase (EH), utilizing 4,5-dihydro-epoxybenzo(a)pyrene as substrate, is presented which may be useful for assaying hair follicles and other small tissue samples with relatively low EH activities. The fluorometric endpoint assay combines the efficient separation of substrate and product with the sensitive fluorometric determination of the product in the ethylacetate fraction. The assay offers the opportunity to investigate the possible interrelationship between EH levels and susceptibility to develop carcinogen-induced cancer. (19 Refs)

50. CARCINOGENICITY AND MUTAGENICITY OF SOME ALKOXY CYCLOPENTA[A]PHENANTHREN-17-ONES: EFFECT OF OBSTRUCTING THE BAY REGION.

Bhatt TS, Hadfield ST, Coombs MM
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Carcinogenesis; 3(6):677-680 1982

Six 11-O-alkoxy derivatives of the phenol 15,16-dihydro-11-hydroxycyclopenta[a]phenanthren-17-one were prepared and tested for their ability to initiate skin tumors on mouse skin after topical application, followed by promotion with croton oil. The 15,16-dihydro-11-hydroxy-11 methoxycyclopenta[a]phenanthren-17-one derivative was the most active, but was less so than the strong carcinogen 15,16-dihydro-11 methylcyclopenta[a]phenanthren-17-one (Ib). The 15,16-dihydro-11-ethoxy-11 hydroxycyclopenta[a]phenanthren-17-one derivative was somewhat less active as a tumor initiator than the 11-methoxy compound, and the 15,16-dihydro-11-hydroxy 11-n propoxycyclopenta[a]phenanthren-17-one and 15,16-dihydro-11-hydroxy-11-n pentoxycyclopenta[a]phenanthren-17-one derivatives were inactive. The 15,16-dihydro-11-hydroxy-11-iso propoxycyclopenta[a]phenanthren-17-one and, surprisingly, the 15,16-dihydro-11-hydroxy-11-n butoxycyclopenta[a]phenanthren-17-one compound possessed weak initiating activity. The phenol, which is too insoluble in organic solvents to be tested in this way, proved to be about half as active as a skin tumor initiator compared with the 11-methyl derivative (Ib) when these compounds were injected sc in oil, and this was followed by topical promotion of dorsal skin remote from the site of injection. 15,16-Dihydro-15-methoxycyclopenta[a]phenanthren-17-one essentially lacked tumor initiating activity on mouse skin, but 15,16-dihydro-15-methoxy-11 methylcyclopenta[a]phenanthren-17-one homologue was moderately active. The carcinogenicity of the 11-alkoxy compounds was in general paralleled by their mutagenicity to Salmonella typhimurium TA100 in the Ames' test, with the exception of the 11-phenol which was not a mutagen under these conditions (plate assay). (Author abstract) (11 Refs)

51. STUDIES ON METABOLISM AND MUTAGENICITY OF NITROSAMINES AND AFLATOXIN B1 IN DROSOPHILA MELANOGASTER (MEETING ABSTRACT).

Hotzer C, Luthy J, Wurgler FE
Institute of Toxicology, CH-8603 Schwerzenbach, Switzerland
Twelfth Annual Meeting of the European Environmental Mutagen Society, June 20-24, 1982, Dipoli. Espoo, Finland. European Environmental Mutagen Society 250 pp., 1982.

In order to compare the activation potency of the xenobiotic-metabolizing enzymes in Drosophila, we carried out experiments with 14C-labelled diethyl-nitrosamine and dimethyl-nitrosamine (DEN and DMN), and with 7 different drosophila strains. The aim of these studies was first to analyze the activation potency of different strains and second, to find a correlation between the metabolism of DEN and its potency to induce mutations. Our results indicate that strains differences exist. We found a good correlation between the DEN metabolism rate, and the mutation frequency induced by DEN. Strains with high activation potency turned out to be more sensitive to mutation induction that strains with low activation potency. These findings are in good agreement with in vitro studies carried out with various tissue slices in mammals. In order to study the xenobiotic-metabolizing enzymes dependent activation of aflatoxin B1 in Drosophila, we treated the strain Hikone-R with 14C-labelled AFB1 and searched for chloroforme soluble metabolites by the Radio-TLC (thin layer chromatography) method. According to our findings, aflatoxicol, the reduced form of AFB1, is the major metabolite in Drosophila. We further found aflatoxin M1, which is metabolized by the MFO and aflatoxin B2a. (no Refs)

52. DIMETHYLNITROSAMINE DEMETHYLASE IN DROSOPHILA MELANOGASTER (MEETING ABSTRACT).

Waters LC, Nix CE, Epler JL
Biology Division, Oak Ridge National Laboratory, Oak Ridge, TN, 37830
Fed Proc; 41(3):1403 1982

DMN, Dimethylnitrosamine is strongly mutagenic in the Drosophila sex-linked recessive lethal mutation test. Studies in other systems suggest that DMN is metabolically activated to its mutagenic form via the action of DMN demethylase, a microsomal, cytochrome P-450 containing mixed-function oxidase. We have characterized such as activity in the Hikone-R strain of Drosophila. Like mammalian DMN demethylases it has many characteristics of a cytochrome P-450-containing mixed function oxidase. Unlike those enzymes, there appears to be only a single form of the enzyme, with an apparent Km of 11 mM, in Drosophila. The enzyme is present in both larvae and adults and in both adult sexes. The enzyme activity, per unit protein, in microsomal preparations from whole larvae or adults is about equal to that found in uninduced rat microsomes. On a cytochrome P-450 basis, the activity, is higher in the fly than in the rat. Although DMN is approximately equally mutagenic in the Hikone-R, Oregon-R, Karsnas, and Samarkand strains of Drosophila, we have detected DMN demethylase only in the Hikone-R strain. (no Refs)

53. COMPARISON OF THE ABILITY OF MOUSE HEPATOCYTES AND MOUSE LIVER S-9 TO ACTIVATE NITROSAMINES AND OTHER CARCINOGENS TO MUTAGENIC FACTORS FOR SALMONELLA TA 1535 (MEETING ABSTRACT).

Kerklaan P, Bouter S, Mohn G
Department of Radiation Genetics and Chemical Mutagenesis, Leiden, The Netherlands
Twelfth Annual Meeting of the European Environmental Mutagen Society, June 20-24, 1982, Dipoli, Espoo, Finland. European Environmental Mutagen Society 250 pp., 1982.

To assay whether homogenization of liver cells during preparation of S-9 results in a reduction of bioactivating properties, hepatocytes from Swiss albino mice were isolated as suspensions of single cells and their biological activity was determined. Mutagen activation kinetics and cell density dependence for mutation induction were measured with cyclophosphamide (CP) and nitrosodimethylamine (NDMA) and optimal conditions for mutagenesis were determined. Under standardized incubation conditions, CP, NDMA and other carcinogens such as nitrosomethylethylamine and 1,2-dimethyldrazine were mutagenic towards TA 1535 in the presence of hepatocytes. Under those conditions, S-9 prepared from the same mouse strain was a less efficient metabolizing system. Nitrosodiethylamine appears not to be significantly activated with any of the two in vitro systems. These results, though preliminary indicate that freshly isolated hepatocytes have greater capacity to activate precarcinogens such as nitrosamines than S-9 preparations do and are, therefore, probably better representative of the in vivo metabolic activity of the liver. (no Refs)

54. INFLUENCE OF GLUTATHIONE ON MNNG INDUCED MUTAGENICITY AND TOXICITY IN YEAST (MEETING ABSTRACT).

Eckardt F, Albers M, Summer KH
Dept. of Radiation Biology, Dept. of Toxicology, Neuherberg, W. Germany
Twelfth Annual Meeting of the European Environmental Mutagen Society, June 20-24, 1982, Dipoli, Espoo, Finland. European Environmental Mutagen Society 250 pp., 1982.

It is assumed that in vivo the alkylating metabolites of MNNG (N-methyl-N'-nitro-N-nitrosoguanidine) are derived predominantly via a thiol mediated pathway. Since glutathione (GSH) is the major non protein thiol compound it is of interest to establish a correlation between cellular GSH content and the mutagenicity and toxicity of MNNG. We investigated stationary (stat) and logarithmically dividing (log) cells of Saccharomyces cerevisiae, D7RAD, and its excision defective derivative D7rad3. It was found: 1) In stat cells GSH content is higher than in log cells. 2) In stat cells MNNG toxicity is 2-3 times higher than in log cells. 3) In log cells MNNG mutagenicity is not generally lower than in stat cells but shows a complicated dose dependence: at 100% survival the mutagenicity of the log cells is 2 fold higher than in stat cells, but in the toxic range of MNNG it is considerably lower. (no Refs)

55. METABOLISM OF N-NITROSO-2,6-DIMETHYLMORPHOLINE (NNDM) BY THE VARIOUS COMPONENT CELLS OF HAMSTER PANCREAS (MEETING ABSTRACT).

Scarpelli DG, Rao MS, Kokkinakis D, Hollenberg P
Department of Pathology, Northwestern University Medical School, Chicago, IL, 60611
Fed Proc; 41(3):927 1982

It has been shown that hamster pancreas contains enzymes which activate the pancreatic carcinogens NNDM and N-nitrosobis(2-oxopropyl)amine (NBOP) to forms which are mutagenic for Salmonella typhimurium. The metabolism of [3H]NNDM by S-9 and microsomal fraction of whole pancreas (WP) and acinar cells (AC) and S-9 of islets (IC) isolated from normal and 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD)-treated pancreas is reported here. Metabolic capacity of duct cells was determined by incubation of pancreas slices in medium containing NNDM in the presence of [3H]-thymidine with and without hydroxyurea to assess unscheduled DNA synthesis (repair). HPLC (high pressure liquid chromatography) analysis showed that S-9, of WP, AC and IC metabolize NNDM to the following compounds in descending order of concentration: HPOP greater than NBOP greater than BHP; NBOP greater than HPOP greater than BHP: and NBOP greater than HPOP greater than BHP. Pretreatment with TCDD increased total metabolism in all circumstances (WP,141%; AC,110% and IC,55%). Microsomes of WP and AC produced the sequence NBOP greater than BHP greater than HPOP. Metabolism by S-9 and microsomes of pancreas was approximately 1/20 of those isolated from liver. In contrast to pancreas, the predominant metabolite produced by liver was HPOP. Unschedules DNA synthesis in nuclei of duct epithelium indicates that these cells are capable of metabolizing NNDM to an active form. (no Refs)

56. ABILITY TO DETECT MUTAGENICITY FOLLOWING NITROSATION OF CHEMICALS IN MOUSE STOMACH (MEETING ABSTRACT).

Solt AK, Neale S
Courtauld Institute of Biochemistry, London, WIP 7PN, England
Twelfth Annual Meeting of the European Environmental Mutagen Society, June 20-24, 1982, Dipoli, Espoo, Finland. European Environmental Mutagen Society 250 pp., 1982.

Nitrosation in the presence of nitrite and gastric juices may provide a source of potential mutagens in vivo. Our ability to detect such mutagenicity was determined with particular reference to drugs used in peptic ulcer management, cimetidine and ranitidine. Mice injected iv with 7 x 10(8) Escherichia coli D494 and administered the required chemical(s) by iv or oral routes were killed at 5 hr. Livers were removed, homogenized and aliquots of suitable dilutions plated to determine the numbers of mutants resistant to ampicillin or total survivors. Dimethylnitrosamine (5mg/Kg) induced similar mutation responses after iv or oral administration and repeated oral doses as low as 47 ng/Kg were detected. However, methylnitrosoguanidine (66 mg/Kg) induced 90% fewer mutations when oral administration, as opposed to iv was used. Precursors of either nitroso compounds, administered orally with nitrite, induced a lower response than the preformed derivative. Cimetidine resembles methylnitroguanidine structurally, its nitrosated derivative induced twice as many E coli D494 AmpR in vitro as equimolar methylnitrosoguanidine but no detectable mutation induction occurred following oral administration of 356 mg/Kg to mice. Cimetidine (3 x 500 mg/Kg) itself did not induce mutations in vivo. (no Refs)

57. EVIDENCE OF ENZYMATIC REDUCTION OF 1-NITROPYRENE BY RAT LIVER FRACTIONS.

Nachtman JP, Wei ET
Chevron Environmental Center, P.O. Box 1272, Richmond, CA, 94802
Experientia; 38(7):837-838 1982

1-Nitropyrene, a mutagenic compound found in diesel exhaust and photocopy toners, is reduced anaerobically by rat liver fractions to 1-aminopyrene. This reaction is stimulated in the microsomal fraction by NADPH and in the cytosol by FMN. Addition of both cofactors produced more reduction in S-9, microsomes, or cytosol than either cofactor alone. (Author abstract) (10 Refs)

58. MUTAGENIC ACTIVATION OF N-HYDROXYPHENACETIN (N-OH-PA) IN THE PRESENCE OF ISOLATED HEPATOCYTES (MEETING ABSTRACT).

Hayashi S, Wirth PJ
National Cancer Institute, Bethesda, MD, 20205
Proc Am Assoc Cancer Res; 23:366 1982

In the Salmonella mutagenesis system N-OH-PA is activated into a mutagen in the presence of microsomal and/or cytosolic fractions from rat liver. In order to evaluate the relative role of metabolic activation vs detoxification in determining the mutagenicity of N-OH-PA, we have investigated the mutagenic activation of N-OH-PA in the Salmonella/hepatocyte system. Incubation of N-OH-PA for 30-60 mins in the presence of hepatocytes and TA 100 resulted in a mutation frequency not significantly different than that of DMSO (dimethyl sulfoxide) control alone. Pretreatment with non-toxic concentrations of diethyl maleate (DEM) for 10 min resulted in a dose dependent depletion of intracellular hepatocyte glutathione (GSH) levels with a greater than 99% depletion following 10 mM DEM. At higher concentrations N-OH-PA was slightly toxic to the bacteria. Pretreatment of the hepatocytes with 0.15 mM salicylamide, an inhibitor of sulfation and glucuronidation, followed by incubation with N-OH-PA in sulfate free medium resulted in dose dependent increase in the mutagenicity of N-OH-PA. The results of these studies indicate that the lack of mutagenicity of N-OH-PA in the Salmonella/hepatocyte system results from a very efficient detoxification of this hydroxamic acid in the intact hepatocyte. GSH is not critically involved in determining the mutagenicity of N-OH-PA in the Salmonella/hepatocyte system. (2 Refs)

59. PSORALENS ARE NOT MUTAGENIC IN THE SALMONELLA ASSAY (MEETING ABSTRACT).

Rao TK, Allen BE, Cox JT
Biology Division, Oak Ridge National Laboratory, Oak Ridge, TN, 37830
Med Pediatr Oncol; 10(1):100 1982

Psoralens are the most notable photosensitizing agents with clinical use for the treatment of skin diseases. Photochemical interaction with the pyrimidine bases of DNA is the basis for their biological activity, which raises the possibility of adverse effects such as toxicity, mutagenicity, carcinogenicity and chromosomal aberrations. Sufficient evidence exists to show that 8-methoxypsoralen (8-MOP), followed by exposure to near UV light (NUV) causes tumors in albino mice, sister chromatid exchange in lymphocytes, and mutations in microbial assays. Psoralens are not adequately studied in the Salmonella assay. Our studies indicated a lack of mutagenic activity for 8-MOP and trioxsalen even when metabolically activated, which is contrary to the report of Bridges and Mottershead that 8-MOP caused frameshift mutations in the dark. Exposure to NUV following treatment with 8-MOP or trioxsalen of stationary or log phase cells did not show mutagenic activity. However, a dose-dependent (7.5-25 x 10(3) J/m2 from a Westinghouse F40BLB lamp) cytotoxicity was noted with strains deficient (TA98 and TA100) for UV-excision repair. Strains capable of UV-excision repair (TA1978 and TA1975) were less sensitive in the cytotoxicity assay. This suggests a genetic nature of the damage. These studies indicate the inability of the Ames Salmonella assay to detect 8-MOP (a possible carcinogen) as a mutagen. (1 Ref)

60. DISPOSITION AND METABOLISM OF THE CARCINOGEN REDUCED MICHLER'S KETONE IN RATS.

McCarthy DJ, Struck RF, Shih TW, Suling WJ, Hill DL, Enke SE
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Cancer Res; 42(9):3475-3479 1982

Studies on the in vivo and in vitro disposition of 4,4'-[14C]methylenebis(N,N-dimethyl)benzamine (reduced Michler's ketone, RMK) were performed. Osborne-Mendel rats retained, after 24 hr, 78% of a po dose of [14C]RMK. At 24 hr after an ip dose, fat, liver, and intestine represented major sites for deposition of radioactivity. The major urinary metabolite of RMK, representing 36% of the total radioactivity recovered in the urine was N,N'-diacetyl-4,4'-(hydroxymethylene)dianiline. In vitro microsomal metabolism of RMK involved demethylation. Products included N,N-dimethyl-4,4'-methylenedianiline, N,N'-dimethyl-4,4'-methylenedianiline, N-methyl-4,4'-methylenedianiline, and 4,4'-methylenedianiline, representing 44.7, 5.3, 11.8, and 6.9%, respectively, of the total radioactivity recovered from the reaction mixture. Although none of the microsomal metabolites was a direct-acting mutagen in the standard Salmonella typhimurium assay, all could be activated to mutagens when incubated with 9,000 x g liver supernatants and reduced nicotinamide adenine dinucleotide phosphate. The activation of 4,4' methylenedianiline to a mutagen suggests that the methyl groups of RMK are not required for the conversion of RMK to a reactive electrophile. (Author abstract) (15 Refs)

61. GENOTOXIC EFFECTS OF SUNLIGHT-ACTIVATED WASTE WATER IN CULTURED MAMMALIAN CELLS.

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JNCI; 69(1):199-203 1982

Cultured Chinese hamster ovary cells were incubated with dilutions of an oil shale retort process water and exposed to natural sunlight. An enhancement of sevenfold to ninefold was seen in photoinduced cytotoxicity (by a colony-forming assay) and mutagenicity [at the hypoxanthine phosphoribosyltransferase (HPRT) locus] for cells pretreated with the process water compared to effects seen in cells exposed to sunlight only. Significant photoinduced cytotoxicity was also observed in cultured human skin fibroblasts when exposed to the process water before being exposed to near UV (NUV) radiation. The mutation frequencies (determined for the HPRT locus) induced by the process water and NUV radiation were as great as those frequencies seen for far UV light alone. Increases in genotoxicity were observed in excision repair-deficient xeroderma pigmentosum skin fibroblasts when compared to the responses seen in normal cells. Risks to health resulting from the phototransformation of these oil shale retort process waste waters are unassessed at this time. (Author abstract) (19 Refs)

BINDING OF CARCINOGENS AND THEIR METABOLITES TO MACROMOLECULES

62. THE ROLE OF CARRIER PROTEINS IN THE OXIDATION OF BENZO(A)PYRENE IN RAT LIVER (MEETING ABSTRACT).

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Fed Proc; 41(3):927 1982

Cytosolic proteins possess the ability to serve as carrier between particulate benzo(a)pyrene (BP) and the microsomal cytochrome P450. The carrier mechanism of the partially purified 46,000-dalton protein (C) was investigated. Using [14C] BP and Sephadex G-100 chromatography, we have demonstrated that (1) the transfer of BP from C to microsomes (M) is predominately in the forward direction, (2) C is capable of recycling between BP and M, (3) BP in isolated BP-M can be oxidized by the addition of NADPH, (4) the oxidized BP (BP*) in M can then be transferred to fresh C in the forward direction, and (5) BP* in M will not dissociate from M without the presence of C. The presence of BP and BP* in various fractions has been shown by HPLC (high pressure liquid chromatography). Thus C can be a carrier for both BP and BP*. The direction of transfer is the same as expected for metabolism of BP in vivo, suggesting that C has such an in vivo role. (no Refs)

63. BENZO(A)PYRENE (BP) BINDING TO CYTOSOLIC PROTEIN ENHANCES ITS MICROSOMAL OXIDATION (MEETING ABSTRACT).

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Fed Proc; 41(3):1730 1982

It is possible that certain cytosolic proteins with adequate binding sites may facilitate the transport of lipophilic carcinogens such as BP to the site of mixed function oxidase action. Sephadex G-100 gel permeation chromatography of rat liver cytosol saturated with 14C-BP resulted in two peaks of protein bound radioactivity. Glutathione-S-transferase (GST) activity (with 1-chloro 2,4 dinitrobenzene and BP-4,5-oxide as substrates) was eluted as a single major peak which coincided with one peak of protein bound BP by microsomes from control or 3-methylcholanthrene pretreated rats was significantly enhanced as compared to ethanol suspended BP. This enhanced formation was not a protein effect since oxidized product formation in the presence of bovine serum albumin or heat denatured protein was not different from that of enthanol-suspended BP. The formation of oxidized products from protein bound BP was time and microsomal protein concentration dependent, required NADPH and was inhibited by the monooxygenase inhibitors alpha -napthoflavone, metyrapone, SKF-525A and 1-benzylimidazole. These results indicate that the presence of soluble proteins in rat liver cytosol having an affinity with BP would facilitate its microsomal tranport from one segment of endoplasmic reticulum to another which allows better microsomal utilization of BP. Coemergence of BP binding protein with GST suggests that the soluble protein could be one of the glutathione S-transferases such as ligandin. (no Refs)

64. COVALENT INTERCALATIVE BINDING OF BENZO(A)PYRENE-9,10-DIOL-7,8-EPOXIDE TO DNA (MEETING ABSTRACT).

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Proc Am Assoc Cancer Res; 23:237 1982

In hamster embryo cells treated with benzo(a)pyrene [B(a)P] covalent binding to nuclear DNA and histone proteins is due to 7,8-dihydroxy-9,10-oxy-7,8,9,10-tetrahydro B(a)P (BPDE). In contrast, another diol-epoxide metabolite 9,10-dihydroxy-7,8-oxy-7,8,9,10-tetrahydro B(A)P (reverse BPDE) apparently binds covalently to non-histone proteins but not to DNA. To explain this difference in specificity, we have used the chemically synthesized anti-isomers of BPDE and reverse BPDE to look for in vitro reaction with purified salmon DNA. We have measured the characteristic fluorescence of the pyrene chromophore in samples of DNA treated with BPDE and reverse BPDE and then repurified to remove non-covalently bound hydrolysis products. With DNA concentration held constant at 50 ug/ml, covalently-bound fluorescence increases linearly with diol-epoxide concentration for both diol epoxides. Binding of reverse-BPDE is about twofold lower than binding of BPDE in what is apparently a single, first-order reaction. The structures of the adducts formed by the two diol-epoxides are very different. Absorbance and fluorescence excitation spectra of reverse-BPDE modified DNA show the 8 nm redshift characteristic of intercalation complexes while BPDE-modified DNA does not. In addition, the BPDE- and reverse-BPDE-modified DNAs exhibit differential susceptibility to acid hydrolysis. Concentrations of Mg++ which block physical intercalation also inhibit covalent binding of BPDE and reserve-

BPDE. Quantitative differences in these in vitro reactions do not account for the differences observed in cell culture. (no Refs)

65. BINDING OF BENZO(A)PYRENE TO HEPATIC CYTOSOLIC PROTEIN ENHANCES ITS MICROSOMAL OXIDATION.

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Biochem Biophys Res Commun; 104(3):1093-1101 1982

A study with 14C-benzo(a)pyrene (BP) indicates that its binding to a protein in rat liver cytosol facilitates its oxidation by microsomal enzymes. Cytosols (100,000 x gravity supernatants) were prepared from the liver of Sprague-Dawley rats. The cytosols saturated with BP were subjected to Sephadex G-100 gel permeation chromatography. Analysis of the fractions resulted in two peaks of protein bound radioactivity. Glutathione-S-transferase activity (towards 1-chlor 2,4-dinitrobenzene as substrate) eluted as a single major peak which coincided with one peak of protein bound BP. Oxidation of cytosolic protein bound BP (GST rich fractions) by microsomes from control or 3-methylcholanthrene-treated rats was significantly enhanced as compared to ethanol suspended BP. Production of oxidized products from the protein bound BP was dependent on incubation time and microsomal protein concentration, it required NADPH and was inhibited by monooxygenase inhibitors (alpha-naphthoflavone, 1-benzylimidazole, metyrapone, and SKF 525A). Coemergence of BP binding-protein with GST suggests that the soluble protein could be one of the glutathione-S-transferases. (15 Refs)

66. BENZO[A]PYRENE METABOLITES: FORMATION IN RAT LIVER CELL-CULTURE LINES, BINDING TO MACROMOLECULES, AND MUTAGENESIS IN V79 HAMSTER CELLS.

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Carcinogenesis; 3(6):635-639 1982

Benzo[a]pyrene was metabolized in liver cell lines derived from BD-IV and BD-VI rats which included several chemically-transformed lines (IAR-6-1; IAR-19; IAR-28), one spontaneous transformant (IAR-27) as well as one nonmalignant line (IAR-20). Cultures were treated with tritiated benzo[a]pyrene over a 5-day period. The cells and medium were extracted with ethyl acetate and the distribution between organic-soluble and water-soluble metabolites determined. Organic-soluble metabolites consisting of dihydrodiols, phenols and quinones were determined by high-pressure liquid chromatography, and macromolecular binding of BP to each cell line was measured over a 24-hr period. Comparisons between binding and overall metabolism were not directly proportional in these liver cell lines. However, there was a positive correlation for benzo[a]pyrene mutagenesis in the V-79 hamster cell assay with 8-azaguanine as a marker when the cell lines with the highest (IAR-20) and lowest (IAR-27) metabolic competence were used as activating cell layers. (Author abstract) (28 Refs)

67. METABOLIC ACTIVATION OF AFLATOXIN B1 AND BENZO(A)PYRENE IN EXPLANT CULTURES OF HUMAN TISSUE (MEETING ABSTRACT).

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Fed Proc; 41(3):330 1982

Binding of aflatoxin B1 (AFB) and benzo(a)pyrene (BP) to DNA was compared in non-tumorous human bronchial (HB), esophageal (HE), colonic (HC), and duodenal (HD) tissues obtained at the time of either surgery or autopsy. Tissues were incubated for 24 hr with radiolabelled AFB or BP at 1.5 M in a chemically defined medium. The binding level of the carcinogens to epithelial DNA varied widely among tissues and individuals. Binding levels of AFB (pmol carcinogen bound to 10 mg DNA) were as follows: HB (mean 16, range 0-92, cases 28); HE (11, 0-35, 11); HC (8, 0-44, 27); and HD (23, 0-46, 11). Binding levels of BP were: HB (25, 0-160, 26); HE (27, 0-104, 11); HC (8, 0-44, 24); and HD (21, 0-58, 10). Thus, the order of mean binding values among the tissues was for AFB: HD greater than HB greater than HE greater than HC, and for BP: HE greater than HB greater than HD greater than HC. In tissues where the metabolism of both carcinogens was studied, binding of BP was generally higher than that of AFB. Analysis revealed no correlation between binding levels of the two carcinogens in any of the tissue types. The results indicate quantitative differences in carcinogen activation among tissues and demonstrate the variation in carcinogen metabolism among individuals. (no Refs)

68. DOSE-RESPONSE FOR BENZO(A)PYRENE METABOLITE-DNA ADDUCTS IN LUNG, LIVER, AND FORESTOMACH OF MICE (MEETING ABSTRACT).

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Fed Proc; 41(3):1548 1982

The formation of benzo(a)pyrene (BP) metabolite-DNA adducts in lung, liver, and forestomach of female A/HeJ mice was examined as a function of BP dose (po) ranging from 2 to 1350 umol/kg. The major identified adduct in each tissue at each dose was the 7beta,8alpha-dihydroxy-9alpha,10alpha-epoxy-7,8,9,10 tetrahydro-BP (BPDEI)-deoxyguanosine adduct. The 7beta,8alpha-dihydroxy-9beta,10beta-epoxy-7,8,9,10 tetrahydro-BP(BPDEII)-deoxy guanosine adduct and a BP-phenol-oxide-DNA adduct were also observed. The dose-response curves for these adducts were sigmoidal in each tissue. The DNA binding expressed as percentage of exposure dose was largest at a BP dose of 0.3 mmol/kg. The dose-response relationships approached linearity at low doses. Thus, the results of these dose-response studies do not reveal the existence of any threshold dose below which binding of BP metabolites to DNA does not occur. Dose-response curves for binding of BP metabolites to protein were also investigated. The ratio of BPDE-DNA adduct levels to protein binding levels was non-linearly related to exposure dose. Thus, binding of BP metabolites to protein cannot be used as a gauge of BP metabolite-DNA binding. These and similar dose-response relationships for polycyclic aromatic hydrocarbons (PAH) metabolite-DNA adducts should be helpful in the low dose extrapolation problem for PAH carcinogenesis. (no Refs)

69. COVALENT BINDING OF PHOTO-OXIDIZED BENZ[A]ANTHRACENE AND RELATED CARCINOGENIC HYDROCARBONS TO PROTEIN.

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Cancer Lett; 16(2):219-225 1982

Formation of unique photo-oxidized products from benz[a]anthracene (BA), 7,12-dimethylbenz[a]anthracene (DMBA), and 3-methylcholanthrene (MC) in the presence of bovine serum albumin (BSA), and their covalent binding to the protein are reported. Fluorescence and excitation spectra of BA photo-products covalently bound to BSA exhibited considerable changes when compared with the parent hydrocarbon BA. At least two distinct photoproducts with overlapping excitation and fluorescence spectra were formed. The excitation spectrum for the 370 nanometer (nm) fluorescence showed the highest peak at 301 nm, whereas for the 390 nm fluorescence the 326 nm peak was the highest. Using the same purification method, BSA with covalently bound DMBA or MC photoproducts was isolated from UV (365 nm)-irradiated DMBA or MC-BSA complexes. Compared to the BA photoproducts, the DMBA photoproduct had less complicated spectra, exhibiting an excitation peak at 320 nm and fluorescence peaks at 377 and 390 nm. In contrast to DMBA, two photoproducts of MC bound to BSA were formed. One photoproduct had fluorescence peaks at 365 and 380 nm with an excitation peak at 320 nm. While the fluorescence characteristics of a phenanthrene-type product from MC were not available, it was expected to have more blue-shifted excitation and fluorescence maxima. The other photoproduct had fluorescence and excitation peaks almost identical with those of MC, suggesting preservation of the original conjugated double bond system. Results suggested that BA, DMBA, and MC can undergo photo-activation and macromolecular binding as in metabolic activation. (19 Refs)

70. INTERACTION OF N-ETHYL-N'-NITRO-N-NITROSOGUANIDINE WITH NUCLEIC ACIDS AND PROTEINS IN COMPARISON WITH N-METHYL-N'-NITRO-N-NITROSOGUANIDINE.

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Chem Biol Interact; 41(1):49-59 1982

Reactivity of N-ethyl-N'-nitro-N-nitrosoguanidine (ENNG) was studied in comparison with N-methyl-N'-nitro-N-nitrosoguanidine (MNNG). The radioactivity of [guanidino-14C]ENNG was incorporated only into the protein fraction and that of [ethyl-14C]ENNG was incorporated into DNA, RNA and protein fractions in ascites hepatoma AH7974 cells, as were those of [guanidino-14C]- and [methyl-14C]MNNG, respectively. The amounts of the binding of ENNG were less than those of MNNG, especially in the incorporation of the ethyl moiety of ENNG into nucleic acid fractions. In a noncellular system, the radioactivity of [guanidino-14C]ENNG was incorporated into proteins, preferentially into basic proteins such as cytochrome c, but was not incorporated into nucleic acids. This behavior is similar to that of [guanidino-14C]MNNG, while the amount of binding of the former was about half of that of the latter. The radioactivity of [ethyl-14C]ENNG was also incorporated into basic proteins to almost the same extent as that of [methyl-14C]MNNG. However, the binding of the ethyl moiety of ENNG to nucleic acids was much lower than that of the methyl moiety of MNNG. Horse heart cytochrome c, bovine pancreatic RNase A and regenerating rat liver chromatin had altered their biological activities to various degrees after modification by ENNG or MNNG. (Author abstract) (25 Refs)

71. ORIGIN AND FORMATION OF 1,7-DIMETHYLGUANOSINE IN TRNA CHEMICAL AND ENZYMATIC METHYLATION.

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Biochim Biophys Acta; 697(3):336-343 1982

The tRNA chemical methylation: (1) 1,7-Dimethylguanosine was found in in vivo methylated tRNA from liver and kidney of rat after exposure to a low dose of dimethylnitrosamine (4 mg/kg body weight). (2) At 4 h after dimethylnitrosamine administration, the 1,7-dimethylguanosine:7-methylguanine ratio (product ratio) for liver and kidney tRNA was 0.017 and 0.091, respectively. At 24 h after dimethylnitrosamine administration, the product ratio was lower in both hepatic and renal tRNA. (3) When dimethylnitrosamine was given in four separate daily injections, the product ratio in hepatic tRNA 4 h after the last dose was the same as for the same total dose given by a single injection, but in renal tRNA it was lower. No dialkyl compound was found in liver and kidney tRNA 24 h after the last multiple injection. tRNA enzymatic methylation: (1) Base analyses of Escherichia coli B tRNA methylated in vitro, by using S-adenosylmethionine as physiological methyl donor and enzyme preparations from liver and kidney of normal rat, indicated that 1,7-dimethylguanosine was also a product of enzymatic methylation. (2) The amount of 1,7-dimethylguanosine formed by kidney enzyme preparation was 3x that produced by the liver extract. (3) A second type of enzymatic methylation assay where chemically methylated tRNA was used as substrate indicated that the 7-methylguanine residues in the nucleic acid are not the substrate of the methylase activity forming the 1,7-dimethylguanosine moieties. Analogous data were obtained for the origin of 1,7-dimethylguanosine residues in tRNA chemical methylation by dimethyl sulfate. (Author abstract) (30 Refs)

72. DOSE- AND CELL CYCLE-DEPENDENT O(6)-METHYLGUANINE ELIMINATION FROM DNA IN REGENERATING RAT LIVER AFTER [14C]DIMETHYLNITROSAMINE INJECTION.

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Cancer Res; 42(9):3814-3821 1982

To study relations between increased transformation sensitivity during DNA synthesis and carcinogen-induced molecular DNA alterations in regenerating liver, the kinetics of formation and the persistence of alkylated DNA bases were determined 10 to 240 min after a single [14C]dimethylnitrosamine (DMN) injection (1.43 and 4.0 mg/kg) during G1 (12 hr after partial hepatectomy) and in synchronized S phase (4 hr after continuous infusion of hydroxyurea after partial hepatectomy; about 80% hepatocytes in DNA synthesis). At 120 min after administration of DMN, the molar fraction of 7-methylguanine reached a maximum which was proportional to the injected DMN dose in G1 but lower by about 25% in S-phase cells. During G1, the molar fraction of O(6)-methylguanine revealed the same formation kinetics as 7-methylguanine; but in S-phase cells, it was reduced by 60% after 1.43 mg/kg and by 35% after 4.0 mg/kg. 3-Methyladenine reached its maximum earlier in S phase than in G1, with a faster decline in S than in G1. As soon as 10 min after DMN was given, the O6-methylguanine/7-methylguanine ratio was significantly lower in S-phase cells than in G1 cells, with a rapid further decrease during 30 min shortly after carcinogen exposure during DNA synthesis. This rapid repair was less expressed after 4.0 mg/kg, indicating an exhaustion of this process after higher carcinogen doses. Cell cycle-dependent differences of the kinetics of O6-methylguanine and 3-methyladenine in DNA in vivo confirm earlier observations in vitro that these adducts are released by different enzymatic mechanisms the activity of which appears to be enhanced during DNA synthesis in rat liver. The faster elimination of the promutagenic O6-methylguanine during DNA synthesis could represent an important but, because of its saturation at higher carcinogen dosages, not sufficiently effective mechanism to protect proliferating cells from initiation during the most critical period of the cell cycle. (Author abstract) (56 Refs)

73. METHYLGUANINES IN LIVER DNA AFTER ADMINISTRATION OF HYDRAZINE TO HAMSTERS (MEETING ABSTRACT).

Bosan WS, Shank RC
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Proc Am Assoc Cancer Res; 23:243 1982

Administration of a hepatotoxic dose of hydrazine (Hz) results in the concomitant formation of 7-methylguanine (7MG) and O6-methylguanine (O6MG) in liver deoxyribonucleic acid (DNA) of rats; evidence has been presented to indicate that the source of the methyl moiety in these bases is S-adenosylmethionine. Young adult, male Syrian golden hamsters were given 90 mg Hz/kg body wt po and killed 0, 0.25, 0.5, 1, 6, 12, 24, 48 and 72 hr later. Liver DNA was fractionated by liquid chromatography, with 7MG and O6MG monitored by their fluorescence at an excitation wavelength of 286 nm. DNA methylation was quantitatively detected 15 min after Hz administration, reached half-maximum levels in approx 1 hr, and maximum levels in approx 6 hr which is in close agreement with results from similar studies in the rat. The rate of removal of 7MG is similar to that seen with dimethylnitrosamine (DMN) in the hamster and Hz in the rat. O6MG persisted longer at max levels in hamster DNA than in rat DNA. The higher levels of O6MG in hamster DNA 24 to 72 hr after Hz administration were not the result of continued DNA methylation since incorporation of radiolabel from [3H-methyl]methionine (3H-MET) given hourly 18 to 24 hr after Hz treatment was greatly diminished compared to incorporation from 3H-MET given 0 to 6 hr after Hz. This study demonstrates the similarity in rates of formation and removal of 7MG and O6MG in liver DNA from Hz-treated rats and hamsters to those in DNA from animals treated with carcinogens which are metabolized to direct alkylating agents, such as DMN. (no Refs)

74. CARCINOGEN BINDING AND DNA REPAIR IN PRIMARY CULTURES OF RAT HEPATOCYTES.

Green CE
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Diss Abstr Int [B]; 42(9):3649-B 1982

The objectives of these studies were to develop an assay with cultured hepatocytes serving as both the metabolizing component and the target cell for cytotoxicity and genotoxicity and to use this system to study three known or suspected carcinogens-senecionine, aflatoxin B1 (AFB1) and aflatoxin M1 (AFM1). Senecionine, a pyrrolizidine alkaloid from Senecio vulgaris, was a potent cytotoxin, as evidenced by the leakage of lactate dehydrogenase from the hepatocytes into the surrounding culture medium and the loss of cells from the monolayer. Senecionine was also genotoxic, stimulating DNA repair. A nontoxic dose of (14C) senecionine was rapidly absorbed by the hepatocytes and converted to more polar metabolites recovered in the culture medium. AFB1 produced by Aspergillus flavus, and a hydroxylated metabolite, AFM1 were both toxic to cultured hepatocytes at very low doses. However, AFB1 was cytotoxic at lower doses than AFM1. The stimulation of DNA repair was apparent at even lower doses than cytotoxicity. AFB1 was again more potent than AFM1, stimulating DNA repair at 0.025 ug/culture, compared to the low genotoxic dose AFM1 of 0.05 ug/culture. The metabolism of a low dose of (14C)AFB1 and (3H)AFM1 by cultured hepatocytes differed significantly. After one hour, only 50% of the (14C)AFB1 remained unchanged in the cultured medium, while 18 hours were required for the same amount of (3H)AFM1 metabolism to occur. (14C)AFB1 and (3H)AFM1 were metabolized to polar metabolites recovered in the aqueous phase after chloroform extraction and to reactive forms which became covalently bound to cellular macromolecules. (no Refs)

75. CHARACTERIZATION AND PROPERTIES OF THE DNA ADDUCTS FORMED BY THE HEPATOCARCINOGEN N-METHYL-4-AMINOAZOBENZENE IN TARGET AND NON-TARGET ORGANS.

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Diss Abstr Int [B]; 42(10):4005-B 1982

The carcinogenic aminoazo dyes, typified by N-methyl-4-aminoazobenzene (MAB), are believed to be metabolized to electrophilic N-sulfonyloxy esters which bind covalently to cellular macromolecules, resulting in the induction of hepatic neoplasia. Since the persistence of DNA-carcinogen adducts has been demonstrated to correlate with the susceptibility of specific tissues to tumor formation, the identity and persistence of the DNA adducts formed by MAB in target (liver) and non-target (kidney and spleen) organs has been determined. In order to produce quantities of adducts sufficient for structural determination, the synthetic ultimate carcinogen, N-benzoyloxy-N-methyl-4-aminoazobenzene (N-BzO-MAB) was reacted in vitro with calf thymus DNA. After enzymatic hydrolysis of the DNA, six MAB-DNA adducts were detected by high pressure liquid chromatographic analysis. In vivo adducts corresponding to all six of the in vitro products were detected after one to five weeks of feeding diets containing 0.06% (3H)MAB. Comparison of the adducts isolated from target and non-target tissues revealed a number of differences during the treatment period; however, the only persistent alteration was the increased levels of 3-(deoxyguanosin-N2-yl)-MAB (N2-dG) in hepatic DNA. N2-dG, therefore, is the adduct most likely to be responsible for the induction of hepatic tumors by MAB. (no Refs)

76. DETECTION OF N2,3-ETHENOGUANINE IN DNA AFTER TREATMENT WITH CHLOROACETALDEHYDE IN VITRO.

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Carcinogenesis; 3(6):663-665 1982

The reaction of chloroacetaldehyde, a reactive metabolite of the carcinogen vinyl chloride, with DNA produces in addition to the hitherto known adducts, 1,N6-ethenoadenine and 3,N4-ethenocytosine, an ethenoguanine adduct, namely N2,3-ethenoguanine. This adduct is formed in the reaction of chloroacetaldehyde with the free base as well. After DNA hydrolysis followed by isolation of this new adduct by hplc, its mass spectrum and fluorescence spectrum are identical with those published in the literature for the chemically synthesized N2,3-ethenoguanine. The formation of only this guanine derivative out of several theoretically possible reaction products allows the formulation of a reaction scheme. The absence of 7-(2-oxoethyl)-guanine, another recently detected DNA adduct of viny chloride, in chloroacetaldehyde-treated DNA suggests its origin from the other reactive metabolite of vinyl chloride, chloroethylene oxide. The potential of N2,3-ethenoguanine to lead to misincorporation of deoxythymidine monophosphate opposite to guanine and the high fluorescence of this adduct provide it with potentially high biological significance and ease of analytical monitoring. (Author abstract) (14 Refs)

ALTERATION OF MIXED FUNCTION OXIDASES BY CARCINOGENS

77. PULMONARY CYTOCHROMES P-450 FROM RABBITS TREATED WITH 3-METHYLCHOLANTHRENE.

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Mol Pharmacol; 22(1):221-228 1982

The effects of pretreatment of rabbits with 3-methylcholanthrene (3-MC: 25 mg/kg/day for 4 days) on the catalytic and spectral properties of lung microsomes were studied, and the chromatographic, spectral, and electrophoretic properties of partially purified pulmonary cytochromes P-450 were compared in 3-MC-treated and untreated rabbits. Treatment with 3-MC caused a 2-fold induction of benzo[a]pyrene hydroxylase activity, but had no effect on ethylmorphine N-demethylase activity. Column chromatographic peaks of two microsomal cytochromes, P-450I and P-450II, were qualitatively and quantitatively similar from both untreated and 3-MC-treated rabbits, but a third peak (cytochrome P-450III) was found only in preparations from treated animals. Both ethyl isocyanide and CO-difference spectral determinations clearly showed that cytochrome P-450III differed from the other two cytochromes. The in vitro stabilities of P-450I and P-450III were similar, and much less than that of P-450II. Sodium dodecyl sulfate-polyacrylamide gel electrophoresis of purified cytochromes P-450 from rabbit lung confirmed the presence of P-450I and P-450II in samples from both untreated and treated animals, and in addition showed a 58,000 mol wt protein associated with the induction of P-450III by 3-MC. P-450I and P-450III are both less stable than P-450II in retaining heme-associated peroxidase activity. (39 Refs)

78. PULMONARY CYTOCHROMES P-450 FROM RABBITS TREATED WITH 3-METHYLCHOLANTHRENE (3-MC) (MEETING ABSTRACT).

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Fed Proc; 41(3):1295 1982

Pretreatment of rabbits with 3-MC caused a consistent increase in total cytochrome P-450 content and benzo(a)pyrene hydroxylate activity, but no change in ethylmorphine N-demethylase activity in lung microsomes. In addition, the CO difference spectrum of the reduced microsomes showed a shift in the Soret maximum. A slight increase in the ratio of 455:430 nm peaks in the ethyl isocyanide difference spectrum of pulmonary microsomes was also observed. Column chromatographic separation of pulmonary cytochromes P-450 demonstrated that 3-MC had no significant effect on the constitutive cytochromes P-450I and P-450II. However, 3-MC induced a new form of this hemeprotein, designated P-450III. The CO difference spectra of cytochromes P-450I, P-450II and P-450III showed absorption maxima at 452, 450 and 448.4 nm, respectively. In addition, the ethyl isocyanide difference spectral properties of cytochrome P-450II had a slower reduction rate and was less stable than P-450III were different from the other two isozymes. At room temperature, cytochrome P-450III had a slower reduction rate and was less stable than P-450II. SDS-PAGE (sodium dodecyl sulfate polyacrylamide gel electrophoresis), analysis revealed that P-450III had a slower electrophoretic mobility than P-450I and P-450II. Following electrophoresis, P-450III and P-450I showed marked decreases in heme-associated peroxidase activity, when compared to P-450II. These studies demonstrate that 3-MC has the ability to induce a new and distinct form of cytochrome P-450 in rabbit lung. (no Refs)

79. KINETIC ANALYSIS OF MIXED FUNCTION OXIDASES (MFO) OPERATIVE IN THE METABOLISM OF BENZO(A)PYRENE B(A)P (MEETING ABSTRACT).

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Fed Proc; 41(3):1548 1982

Environmental influences of aryl hydrocarbon hydroxylase (AHH) activity of hepatic microsomes using B(a)P as substrate is complicated by the fact that B(a)P is metabolized via several pathways. We have investigated the kinetics of AHH over a substrate concentration range (0.001 to 11.98 uM) using microsomes from mice subjected to dietary stress [fat-free (FF), 20% corn oil (HF)], pretreatment with the inducer, phenobarbitol and/or the carcinogen, B(a)P and N-nitrosodimethylamine (DMN). Breaks in Lineweaver-Burk plots occurred depending on diet, drug or carcinogen pretreatment and were influenced by pH and temperature. Maximum efficiency of B(a)P hydroxylation (comparison of catalytic constants) occurred at pH 7.0 for the HF Pb group, at pH 6.5 for FF and FFPb groups, and at pH 7.4 for non-induced mice fed HF diet. As expected mice receiving HF diet and Pb metabolized B(a)P most effectively (17X FF control). Pretreatment of mice with DMN and B(a)P DMN resulted in an inability to detect kinetics in the low concentration range (.001-.170). Breaks in Arrhenius plots occurred using microsomes from all mice except those in FF Pb group (0-58C). Energies of activation using microsomes from FF, FFPb, HFPb (low concentration) and FFPB (high concentration) were 16,370 +/-1473 cal/mole. This form of kinetic analysis may be used to identify individual MFO enzymes. (no Refs)

80. EFFECTS OF CYCLOPHOSPHAMIDE AND POLYCYCLIC AROMATIC HYDROCARBONS ON CELL GROWTH AND MIXED-FUNCTION OXIDASE ACTIVITY IN A HUMAN COLON TUMOR CELL LINE.

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Cancer Res; 42(9):3676-3681 1982

Human colon tumor cells (cell line LS174T) retain a cytochrome P-450-containing drug metabolism system capable of hydroxylating polycyclic hydrocarbons and the anticancer drug cyclophosphamide. The hydroxylation of benzo(a)pyrene by human colon tumor cells is highly inducible. Phenobarbital plus hydrocortisone induce benzo(a)pyrene hydroxylation activities 10-fold, while benz(a)anthracene induces the rate of hydroxylation 30-fold. Cytochrome P-450 specific content is increased two- to three-fold by treatment with phenobarbital plus hydrocortisone and benz(a)anthracene, respectively. Addition of cyclophosphamide alone results in no increase in hydroxylation activities but causes a decrease in cell growth rate. The combination of cyclophosphamide with either of the inducers phenobarbital plus hydrocortisone or benz(a)anthracene results in markedly enhanced inhibition of cell growth as judged both by a decrease in the number of cells per plate and in the incorporation of [3H]thymidine into DNA. Thus, these data show that cyclophosphamide is cytotoxic to human colon tumor cells and that the cytotoxicity is enhanced by simultaneous administration of benzo(a)anthracene or phenobarbital plus hydrocortisone to the tissue cultures. (Author abstract) (36 Refs)

81. 2-ACETYLAMINOFLUORENE (AAF) DEPENDENT INCREASES IN EPOXIDE HYDROLASE: SPECIES, STRAIN AND SEX DIFFERENCES (MEETING ABSTRACT).

Graichen ME, Dent JG
Chemical Industry Institute of Toxicology, Research Triangle Park, NC, 27709

Toxicologist; 2(1):101 1982

Exposure of rats to hepatocarcinogens causes substantial increases in hepatic microsomal expoxide hydrolase (EH) activity. The potency of compounds in increasing EH is related to their carcinogenic potency. The objective of this study was to investigate the relationship between hepatocarcinogenicity and increases in epoxide hydrolase using the known species, strain and sex differences in susceptibility to AAF carcinogenicity. Following administration of AAF in the diet or via ip injections, liver microsomes or 10,000 g supernatant was prepared. EH activity was measured with benzo(a)pyrene-4,5-oxide as substrate. Three daily ip injections of AAF, at doses between 5 and 80 mg/kg/day, caused dose-related increases in EH in male F-344 and CD rats. The log-linear dose response obtained has the same slope in both strains and the ED50 was 13 mg/kg/day. The maximum increase observed was 350% of control activity in both strains. No increase in EH activity was detected in guinea pigs treated with AAF at doses between 40 and 240 mg/kg/day for 3 days. In DBA2 and C57Bl6 mice fed 0.02% AAF for 2 weeks, decreases in EH were observed. By comparison, F-344 male rats fed this diet exhibited a 460% increase in EH activity. Female rats, mice and guinea pigs are poor N-hydroxylators of AAF and are resistant to the carcinogenic action of AAF. (no Refs)

82. A CYTOCHROME P-450 ISOZYME WITH HIGH AFFINITY FOR DIMETHYLNITROSAMINE: INDUCTION BY PYRAZOLE AND OTHER NITROGENOUS COMPOUNDS (MEETING ABSTRACT).

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Fed Proc; 41(3):1402 1982

Treatment of rats with pyrazole and other nitrogenous compounds elevated the hepatic microsomal dimethylnitrosamine demethylase activity (DMNd). The highest inducton was observed with pyrazole. DMNd was induced 3-4 fold but some classical monooxygenase activities were not induced. The increased DMNd was accompanied by the appearance of a new microsomal protein shown as a 52,000 dal band in polyacrylamide gel electrophoresis. This protein species was decreased by in vivo treatment with CoCl2 which also decreased DMNd, suggesting the involvement of a hemoprotein in the induction. The DMNd of the pyrazole-induced microsomes showed a Km of 61 uM and Vmax of 12.1 nmol/min/mg which were clearly different from those of the control microsomes. Limited tryptic digestion cleaved the active site of NADPH-cytochrome P-450 reductase and also decreased the microsomal DMNd. The DMNd was regained by preincubating the microsomes with purified reductase. This indicates that the reductase is an essential component enzyme of the DMNd in both the control and pyrazole-induced microsomes. The results suggest that pyrazole induces a P-450 isozyme which has high affinity and turnover for dimethylnitrosamine and probably for other nitrosamines. (no Refs)

83. KINETIC EVIDENCE FOR THE INVOLVEMENT OF MULTIPLE FORMS OF CYTOCHROME P-450 IN THE METABOLISM OF ACETYLAMINOFLUORENE (AAF) (MEETING ABSTRACT).

McManus ME, Minchin RF, Sanderson N, Wirth PJ, Thorgeirsson SS
National Institutes of Health, Bethesda, MD, 20205

Fed Proc; 41(3):1402 1982

In order to initiate carcinogenesis AAF requires metabolic activation. N-Hydroxylation is considered to be obligatory for this activation while ring hydroxylations appear to be detoxification pathways; all these reactions being cytochrome P-450 dependent. For an estimate of the significance of these pathways in the metabolism of AAF, a kinetic study was undertaken using rat liver microsomes and substrate concentrations ranging from 0.02-200 uM. N-Hydroxylations accounted for approximately 50% of the metabolites at low substrate concentrations (less than 0.2 uM) but less than 5% at concentrations of AAF above 10 uM. The Km and Vmax for this reaction were 0.04 uM and 5.95 pmoles/min/mg respectively. While N-hydroxylation was best described by a single enzyme system, two enzyme kinetics were observed for 1, 3, 5 and 7 hydroxylations. For example, Hofstee plots revealed a high affinity low capacity (4.87 pmoles/ min/mg) enzyme and a low affinity high capacity (1289 pmoles/min/mg) enzyme for the 7-hydroxylation of AAF. These data indicate that more than one form of cytochrome P-450 is involved in each of the ring hydroxylations, whereas only one form catalyzes the N-hydroxylation. (no Refs)

84. 3-METHYLCHOLANTHRENE INDUCES PHENOBARBITAL-INDUCED CYTOCHROME P-450 HEMOPROTEIN IN FETAL LIVER AND NOT CYTOCHROME P-448 HEMOPROTEIN INDUCED IN MATERNAL LIVER OF RATS.

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Biochem Biophys Res Commun; 107(1):6-11 1982

Absorption characteristics of drug-metabolizing enzymes in fetal rat liver following various induction regimens was investigated. The aminopyrene (AM) and hexobarbital (HB)-metabolizing activities of fetal liver microsomes on day 21 of pregnancy were induced by 3-methylcholanthrene (3MC) administered on day 18 and 19 of pregnancy. No inductive effect was observed in the maternal microsomes. These results suggested that the inductions of the AM- and HB-metabolizing activities occurred only during the fetal period. No inductive effect of 3MC on AM- and HB-metabolizing activities was observed in newborn liver microsomes following fetal administration of 3MC. The disappearance of 3MC inducing effects at birth suggested that a hemoprotein different from that induced in maternal liver microsomes was induced in fetal liver microsomes by maternal administration of 3MC. Maximum carbon monoxide difference spectra of cytochrome P-450 from 3MC-pretreated maternal liver yielded a peak at 448 nanometer (nm), compared to 450 nm for fetal liver microsomes. The hemoprotein induced in fetal liver by 3MC appeared to be the same as that induced in maternal liver by phenobarbital. (16 Refs)

ALTERATION OF OTHER CARCINOGEN-METABOLIZING ENZYMES BY CARCINOGENS

85. INCREASED URIDINE DIPHOSPHATE-GLUCURONYLTRANSFERASE ACTIVITY IN PRENEOPLASTIC LIVER NODULES AND MORRIS HEPATOMAS.

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Cancer Res; 42(9):3747-3752 1982

In preneoplastic rat liver nodules produced by 2-acetylaminofluorene, certain uridine diphosphate-glucuronyltransferase (UDP-GT) activities, which are ascribed to a distinct enzyme form, were selectively increased (5-fold). This enzyme form, operationally termed UDP-GT1, accepts 1-naphthol,4-methylumbelliferone, and 3-hydroxybenzo(a)pyrene as substrates and is chiefly inducible in liver by 3-methylcholanthrene-type inducers. Glucuronidation of other substrates (morphine, 4-hydroxybiphenyl, chloramphenicol, bilirubin, and estrone) was only slightly enhanced or decreased in nodular tissue. Differentially increased UDP-GT1 activities were also found in Morris hepatomas 9121 and 7777. Rabbit antibodies to rat liver UDP-GT1, purified from 3-methylcholanthrene-treated rats, demonstrated immunological similarity between the enzymes from liver, nodular tissue, and Morris hepatoma 9121. Rocket immunoelectrophoresis ascertained that enhanced enzyme activity in nodular tissue reflected an increased level of enzyme protein. Increased activity of UDP-GT1 together with decreased cytochrome P-450-dependent monooxygenase may contribute to the resistance of preneoplastic hepatocytes to the cytotoxic actions of chemical carcinogens. (Author abstract) (43 Refs)

86. THE INDUCTION OF THE D-T DIAPHORASE AND THE NAD(P)H-NITRO BT REDUCTASE BY CARCINOGENIC POLYCYCLIC HYDROCARBONS IN THE SPLEEN AND LYMPH NODES OF THE RAT (MEETING ABSTRACT).

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Fed Proc; 41(3):330 1982

The polycyclic hydrocarbons 3,4-benzpyrene, 7,12-dimethylbenzanthracene and 3-methyl cholanthrene induce the activity of the soluble enzyme D-T diaphorase in rat spleen and lymph nodes. The dehydrogenation of NAD(P)H in fractions sedimented at 8000 and 100000 g in the same animals is not affected by the treatment. The induction of the soluble diaphorase is dose dependent and is inhibited by dicumarol. The histochemical activity of the NAD(P)H-NBT reductase is also induced by carcinogens, this enzyme is localized in histiocytes and T lymphocytes; B lymphocytes, even after the administration of carcinogens, show a very weak activity. The staining of the NAD(P)H-NBT reductase is not specific for the D-T diaphorase but the negative effects of the carcinogens on the particulate enzymes suggest the observed increase in histochemical activity may be due to the D-T diaphorase. These results seem to indicate that a) lymphoid organs participate actively in the metabolism of carcinogens, b) this function may be specific for histiocytes and T lymphocytes, and c) the inductive histochemical and biochemical action of carcinogens may be another useful and reliable parameter to differentiate B and T lymphocytes in experimental animals. (no Refs)

87. THE EFFECTS OF RIBOFLAVIN DEPLETION AND 3-METHYLCHOLANTHRENE TREATMENT ON HEPATIC AZOREDUCTASE AND D.T. DIAPHORASE (MEETING ABSTRACT).

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Fed Proc; 41(3):357 1982

Hepatic azoreductase and DT diaphorase are involved in the metabolism of xenobiotics and carcinogens. Both enzymes are flavoproteins and induced by 3-methylcholanthrene (3MCA). The effect of riboflavin deficiency on hepatic levels of these enzymes and their inductions by 3MCA was examined in male Sprague-Dawley rats fed a deficient diet for 6 weeks. Controls received deficient diet supplemented with riboflavin in the drinking water (20 ug/ml). 3MCA was injected ip daily for three days prior to sacrifice (10 mg/kg). Both enzymes were predominantly located in the cytosol where riboflavin deficiency resulted in a 41.9% decrease in azoreductase and a 59.6% decrease in diaphorase. Microsomal diaphorase and azoreductase were only slightly decreased. 3MCA resulted in a 10 and 14 fold increase in cytosolic azoreductase and diaphorase in controls, whereas deficient rats elicited a 13 and 20 fold increase in the activity of these enzymes. Both cytosolic enzymes were inhibited 60% by Warfarin in control rats. Warfarin inhibition increased to greater than 90% in cytosols from 3MCA treated rats. Microsomal azoreductase and DT diaphorase were increased 4 and 2 fold respectively by 3MCA. These results indicate that riboflavin deficiency does not inhibit the induction of azoreductase and diaphorase by 3MCA. (no Refs)

88. TRANSPLACENTAL EFFECTS OF CARCINOGENIC AND NONCARCINOGENIC SUBSTANCES ON THE PYRUVATE KINASE (PK) AND LACTATE DEHYDROGENASE (LDH) ACTIVITIES OF THE MOUSE LUNG AND ON THE LDH ISOENZYME SPECTRUM.

Rady P, Arany I, Uzvolgyi E, Bojan F, Kertai P
Kozegeszsegtani es Jarvanytani Intezet, Debreceni Orvostudomanyi Egyetem, Debrecen, Hungary
Magy Onkol; 26(2):153-161 1982

The effects of carcinogenic and noncarcinogenic substances, administered ip on day 18 of pregnancy, on the PK and LDH activities and on the H/M isoenzyme ratio of LDH in the lungs were studied in the offspring of CFLP mice on day 19 of intrauterine life and on days 1-35 of extrauterine life, ie, before the manifestation of lung tumors. The substances administered included the carcinogens urethane (UR: 1,000 mg/kg), 3-methyl-cholanthrene (MC: 10 mg/kg) and dimethylnitrosamine (DMN: 10 mg/kg); noncarcinogenic analogs of carcinogens: phenylurethane (PHU: 100 mg/kg) and pyrene (20 mg/kg), and paraquat (PAR: 20 mg/kg), a noncarcinogenic substance toxic for the lungs. UR, MC and DMN were found to increase the PK and LDH activities in the lungs already on day 19 of intrauterine life. The enzyme activities showed further increases during the first days of extrauterine life to decline beginning from day 7 of life, but still being significantly increased on day 35. Unlike the noncarcinogenic analogs, PAR was found to cause a transient increase in the PK and LDH activities during the intrauterine and extrauterine lives. The H/M isoenzyme ratio of LDH was reduced by UR, and the reduction was still significant on day 35. The H/M ratio was transiently reduced by PAR, while PHU, the only noncarcinogenic analog tested in this respect, caused no change in the isoenzyme ratio. (28 Refs) (In HUN)

89. CHANGES IN ALDEHYDE DEHYDROGENASE PHENOTYPE DURING THE PROMOTION PHASE OF RAT HEPATOCARCINOGENESIS (MEETING ABSTRACT).

Wischusen S, Evces S, Lindahl R
University of Alabama, Tuscaloosa, AL, 35486
Proc Am Assoc Cancer Res; 23:228 1982

Hepatomas induced in post-weaning male Sprague-Dawley (SD) rats by sequential dietary 2-acetylaminofluorene (AAF)/phenobarbital (PB) exposure possess and aldehyde dehydrogenase (AlDH) phenotype qualitatively and quantitatively different from that of normal liver. To assess the generality of this phenotype, we have evaluated the ability of other carcinogens and tumor-induction protocols to induce this change. One day old female SD rats were injected ip with either diethylnitrosamine (DEN) or AAF (0.15 uM/gm body wt in corn oil). Animals were weaned onto a 30% protein diet containing 0.05% PB. At intervals up to 18 weeks after weaning, rats were killed and the AlDH phenotype of both normal liver and tumors characterized as outlined below. The NADP-dependent, benzaldehyde-oxidizing, tumor-specific AlDHs were not detected in any normal liver by total activity assays, gel electrophoresis or electrofocusing, or by immunochemical methods. However, a significant change in AlDH phenotype, characterized by high activity with propionaldehyde and NAD was observed in normal liver of some animals receiving PB following either DEN (3/12 by 8 wks) or AAF (5/12). No animals receiving only PB (0/9) nor the basal diet show this change. The new activity is distinguishable from the normal liver AlDHs, and from the tumor-specific and TCDD-inducible isozymes in a number of functional and physical properties, but appears to be closely related to previously described PB-inducible AlDH. (no Refs)

90. LACK OF AVAILABILITY OF ENDOGENOUS RETINYLPHOSPHATE FOR MANNOSYLRETINYLPHOSPHATE SYNTHESIS IN MICROSOMES FROM HEPATOMA TISSUE (MEETING ABSTRACT).

De Luca LM, Silverman-Jones C, Brugh M
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Fed Proc; 41(3):861 1982

Rat liver microsomes synthesize mannosylretinylphosphate (MRP) and dolichylmannosylphosphate (DMP) from endogenous lipid acceptors. The ratio of MRP to DMP synthesized in 15 min at 37 C in the presence of bovine serum albumin and 5 mM $MnCl_2$ is about one to four. The amount of endogenous retinylphosphate available for mannosylation is about 3.24 pMoles or 1.2 ng and the amount of endogenous dolichylphophate about 13.3 pMoles or 20 ng per mg protein after 15 min at 37 C. The presence of $MnCl_2$ is essential for MRP but not the DMP synthesis. Microsomes from a transplantable rat hepatoma, induced in vivo with methyl-acetoxymethyl nitrosamine, failed to synthesize detectable levels of MRP at least at 0, 5, 10 and 25 mM $MnCl_2$, in the presence of normal levels of DMP synthesis. However, when exogenous RP was supplied, it was utilized as an acceptor of mannose by hepatoma microsomes, albeit to a lesser extent than by rat liver microsomes. Similar results were obtained in microsomes from a transplanted guinea pig hepatic carcinoma (Line 10) induced in vivo by diethylnitrosamine feeding. Thus, it seems that hepatoma tissue lacks endogenous retinylphosphate, even though it contains the enzyme for MRP synthesis. (no Refs)

91. RAPID DECREASES IN N-HYDROXY-2-ACETYLAMINOFLUORENE SULFOTRANSFERASE ACTIVITY OF LIVER CYTOSOLES FROM RATS FED CARCINOGEN (MEETING ABSTRACT).

Ringer DP, Kampschmidt K, King RL, Jackson S, Kizer DE
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Fed Proc; 41(3):927 1982

Sulfation of N-hydroxy-2-acetylaminofluorene (N-OH-AAF) yields a candidate ultimate carcinogen for hepatocarcinogenesis in rats. Employing an assay for N-OH-AAF sulfotransferase described by Mulder et al, we monitored this activating pathway during the initial phase of hepatocarcinogenesis produced by feeding rats a diet of 0.05% AAF. Our studies revealed an immediate and precipitous decrease (4-5-fold) in N-OH-AAF sulfotransferase activity following 1 to 5 days of feeding, and activity remained at low levels with continuous feeding of AAF diet throughout 4 weeks. Other known carcinogens, eg, aflatoxin, diethylnitrosamine and thioacetamide, caused equally significant drops in N-OH-AAF sulfotransferase activity by 7 days of feeding, while non-carcinogenic compounds, eg, p-aminoazobenzene, fluorene and sodium barbital, failed to reduce N-OH-AAF sulfotransferase activity. Parallel monitoring of rat serum GOT (glutamic oxalic-acetic) activity during AAF-induced decreased sulfotransferase activity failed to indicate appreciable hepatocellular toxicity. Perhaps N-OH-AAF sulfotransferase activity can be used as an early indicator of hepatocarcinogenesis. (no Refs)

92. SIALIC ACID METABOLISM IN NUTRITIONALLY-MODULATED HEPATOCARCINOGENESIS (MEETING ABSTRACT).

Fox OF, Kishore GS, Graham SA, Carubelli R
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Fed Proc; 41(3):337 1982

The sialic acid content and the activities of the enzymes responsible for the activation, transfer and hydrolysis of sialic acid were investigated in the livers of male Sprague-Dawley rats treated with 2-acetylaminofluorene (AAF). Basal diets containing 20% corn oil, 18% coconut oil + 2% linoleic acid, or 2% linoleic acid with or without supplementation with 0.7% (w/w) butylated hydroxytoluene (BHT), were used. The carcinogenic diets contained 0.05% (w/w) AAF. AAF-treated rats and age-matched controls fed basal diets, were killed after 14-17 weeks of treatment. The livers were used for histological, chemical and enzymological studies. Rats fed high-fat diets showed earlier and higher incidence of AAF-induced hyperplastic nodules (HPN); BHT supplementation greatly retarded the development of these lesions. Increases in sialic acid content and in the levels of CMP (cytosine monophosphate)-sialic acid synthetase and neuraminidase, both cytosolic and particulate, were observed in the livers from AAF-treated rats. Sialyltransferase activity, on the other hand, was not affected. BHT supplementation resulted in lower levels of sialic acid and CMP-NANA synthetase in rats fed low fat and saturated-fat diets; proportional reductions were observed in AAF-treated and in control rats. The chemical and enzymatic changes observed in AAF-treated rats are consistent with an increased turnover of sialoglycoconjugates during the carcinogenic process. (no Refs)

93. HEPATOTOXIC AND CANCEROUS ACTIVATION OF GAMMA-GLUTAMYLTRANSFERASE IN RAT LIVER (MEETING ABSTRACT).

Fiala S, Payne RR, Trout EC, Kettering WG, Fiala A
Cell Physiology Laboratory, Veterans Administration Medical Center, Martinsburg, WV, 25401
Med Pediatr Oncol; 10(1):103 1982

Hepatotoxic compounds benzyl chloride, gamma-hexachlorocyclohexane, carbon tetrachloride, and the pesticide Kerb, and carcinogenic 3'-Me-DAB, administered to Sprague-Dawley male rats in one or two large doses, produced in 24 hrs a striking increase in the liver of the activity of gamma-glutamyl transferase (GGT) and a definite increase of total DNA. An increase in the number of GGT (+) hepatocytes was detected histochemically. In contrast to the induction by 3'-Me-DAB of simultaneous increases of GGT and of the glutathione (GSH) concentration during the period of 24-48 hrs, the increase of GGT produced by hepatotoxic compounds was accompanied by a decrease of GSH which forced GGT to return in 48 hrs to initial values. In hypophysectomized rats hepatotoxic compounds and 3'Me-DAB produced an increase of GGT which rapidly fell to the initial level without any substantial change in the concentration of GSH. From these experiments we concluded that: 1) Increase of GGT alone is not a specific effect of hepatocarcinogens in rat liver, but can be produced by various compounds which are toxic to liver tissue; 2) Not GGT alone, but only the combination of GGT with GSH is the Marker of rat liver carcinogenesis; 3) 3'-Me-DAB inactivates the feedback which keeps the levels of GSH and of GGT constant at the normal values; 4) Hepatotoxic compounds, as long as they do not damage the GSH-GGT feedback, are not carcinogenic for rat liver; 5) In hypophysectomized rats 3'-Me-DAB does not produce tumors because in their livers it is only hepatotoxic and does not become carcinogenic. A model will be proposed of GSH-GGT feedback, its nature, and function. Hepatotoxic effect of a compound has a relatively low affinity for vital receptors and can easily be removed, so that they are not permanently changed. The cancerous effect concerns receptors not essential to the life of the cell and involved in the social rather than the vital functions. The affinity for their receptors is high. (no Refs)

94. INDUCTION OF ORNITHINE DECARBOXYLASE ACTIVITY IN MOUSE URINARY BLADDER BY L-TRYPTOPHAN AND SOME OF ITS METABOLITES.

Matsushima M, Takano S, Erturk E, Bryan GT
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Cancer Res; 42(9):3587-3591 1982

The responses of female noninbred mouse urinary bladder ornithine decarboxylase (EC 4.1.1.17) (ODC) and S-adenosyl-L-methionine decarboxylase (EC 4.1.1.50) (SAND) activities to L-tryptophan feeding and to topical intraurethral administration of L-tryptophan and some of its urinary metabolities were studied. Mice fed a diet containing 1% L-tryptophan demonstrated significant increases in vesical ODC and SAMD activities as early as 2 wk after the commencement of the diet. By the end of the 3rd wk, ODC and SAMD activities reached peak values of seven- and three-fold, respectively, significantly greater than the control levels (p less than 0.05 and p less than 0.01, respectively). Then, enzyme activities gradually decreased but remained at levels significantly higher than those of the control mice until the end of the 6th wk when the study was terminated. Topical application by urethral catheter of some urinary tryptophan metabolites was followed by a rapid, transient induction of urinary bladder ODC activity within 5 hr. Statistically significant differences between vehicle controls and xanthurenic acid (p less than 0.01), DL-kynurenine (p less than 0.01), L-kynurenine (p less than 0.01), anthranilic acid (p less than 0.01), and quinaldic acid (p less than 0.05) were observed. However, no significant differences were seen with L-tryptophan, 3-hydroxy-DL-kynurenine, the 8-methyl ether of xanthurenic acid, or D-kynurenine or with 3-hydroxyanthranilic, kynurenic, quinolinic, picolinic, and nicotinic acids. Bladder SAMD was not elevated significantly by most of these directly applied tryptophan metabolites. ODC inducibility by active compounds was followed by mucosal hyperplasia within 7 days. These data suggest that certain L-tryptophan metabolites may be involved in two-stage urinary bladder carcinogenesis in a manner similar to that shown to occur in murine skin tumor systems by other chemicals. (Author abstract) (40 Refs)

95. ORNITHINE DECARBOXYLASE INDUCTION IN RAT COLON: SYNERGISTIC EFFECTS OF INTRARECTAL INSTILLATION OF SODIUM DEOXYCHOLATE AND STARVATION-REFEEDING (MEETING ABSTRACT).

Stanley BA, Kazarinoff MN
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Fed Proc; 41(3):355 1982

Starvation-refeeding, intrarectal instillation of the known colon tumor promoter sodium deoxycholate (NaDC), and a combination of starvation-refeeding with NaDC instillation were compared for their effects on ornithine decarboxylase (ODC) activity in the colon of male Sprague-Dawley rats. Starvation (48h) and refeeding (12h) led to a 5-fold increase in

ODC levels compared to ad lib fed controls, while NaDC (24mM) led to a 3-fold rise in ODC levels 4.5 after instillation. The combination of the two treatments gave a synergistic 16-fold increase over controls. Complicating effects of immediate food consumption were avoided by removing food 6h before sacrifice of all groups. Starvation-refeeding also induced rat liver ODC, but synergism with thioacetamide or dexamethasone, known inducers of liver ODC, was not seen. The synergism observed in colon may indicate that the treatments act via different mechanisms to induce ODC. Our working hypothesis is that the increased ODC level seen after starvation-refeeding reflects an increase in general macromolecular synthesis, while the increased ODC level seen after NaDC instillation reflects a specific increase in ODC synthesis. The synergistic enhancement of tumor promoter-related ODC induction by a dietary pattern (rather than a dietary component) suggests a new area for investigation of potential nutrition-cancer interactions. (no Refs)

REVIEWS AND OTHER RELEVANT STUDIES

96. GENETIC EFFECTS OF N-METHYL-N'-NITRO-N-NITROSOGUANIDINE AND ITS HOMOLOGS.

Gichner T, Veleminsky J
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Mutat Res; 99(2):129-242 1982

The chemistry and metabolism of N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) and derivatives of MNNG are reviewed. The mode of interaction of MNNG with DNA and proteins are described. Genotoxic effects on microorganisms, plants, and animals are discussed, including effects on human cells in vitro. Data on carcinogenicity and teratogenicity of MNNG and on genotoxicity of MNNG-homologs are presented. (977 Refs)

97. PREDOMINANCE OF A CELL POPULATION LESS SENSITIVE TO CARCINOGENESIS IN NEOPLASTIC CELLS OF 3-METHYLCHOLANTHRENE-INDUCED TUMORS IN MOUSE AGGREGATION CHIMERAS.

Elbling L, Sauermann G
Inst. Cancer Res., Univ. Vienna, Borschkegasse 8a, A-1090 Vienna, Austria
Cancer Res; 42(9):3486-3491 1982

Tumors were induced by im injection of 3-methylcholanthrene (0.5 mg) in 100% experimental aggregation chimeras derived from two mouse strains C57BL/6J (hereafter called B6) and A/J, dimorphic for the enzyme glucosephosphate isomerase (Gpi-1a or Gpi-1b) and differing in coat color, aryl hydrocarbon hydroxylase inducibility, and cytotoxic activities of natural killer cells and macrophages. In the majority of host tissues and organs, such as coat, lung, spleen, and skeletal muscle, the B6 phenotype was predominant. Likewise, the nonneoplastic intratumoral host cells of both induced primary tumors and parental tumor transplants in chimeras were of B6 origin. In contrast, neoplastic cells in 70% of the tumors originated exclusively from the less aryl hydrocarbon hydroxylase-inducible and less immune competent A/J strain. The A/J origin was verified by subsequent cell culturing of the tumors. Only 30% of the tumors contained neoplastic cells of both A/J and B6 phenotype. A further reduction of mixed tumors was achieved with lower doses (0.1 and 0.06 mg) of the carcinogen. The dominance of the A/J phenotype of the tumors contrasted not only with aryl hydrocarbon hydroxylase inducibility and host cell composition but also with tumor pathogenesis (at 0.5 mg 3-methylcholanthrene) in the parental strain. Whereas tumor incidence was 100% in the B6 strain, it was only 65% in A/J mice, with tumors also developing later. As the in vivo and in vitro growth rates of parental strain-derived tumors were comparable, a cell selection caused by different growth rates favoring the A/J phenotype appeared unlikely. (Author abstract) (27 Refs)

98. HUMAN METABOLIC VARIABILITY IN XENOBIOTIC BIOTRANSFORMATION. IMPLICATIONS TO GENOTOXICITY (MEETING ABSTRACT).

Pelkonen O

Department of Pharmacology, SF-90220 Oulu 22, Finland

Twelfth Annual Meeting of the European Environmental Mutagen Society, June 20-24, 1982, Dipoli, Espoo, Finland. European Environmental Mutagen Society 250 pp., 1982.

Most mutagens and carcinogens are inactive per se. They are converted into reactive forms by the organism's own enzymes. The inactivation of reactive intermediates is also performed enzymatically. It seems that the balance between activating and detoxicating enzymes is an important determinant in the extent of interaction between reactive intermediates and the DNA. If the activity and/or balance of activating and/or detoxicating enzymes is rate-limiting for the over-all process of genotoxicity, it would be of a great theoretical and practical interest to know factors affecting these activities. The variability of xenobiotic metabolism is very large. Measurements on in vitro tissue preparations or on cells in culture have shown even 100-fold interindividual differences in enzyme activities. Studies in experimental animals imply, and human studies strongly suggest, that activity and inducibility of these enzymes is determined, to a large extent, by the genetic background of an individual. Non-genetic factors (nutrition, chemicals, diseases etc) then modify genetically-determined basal activities and increase the variability. In most cases it is not possible to estimate the relative contributions of genetics and environment to the variability of xenobiotic metabolism. (no Refs)

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Swenberg JA, Zimmerman HM, Maltoni C, Kurland L, Laerum OD, Kleihues P, Selikoff I, Heidelberger C
Chemical Industry Inst. Toxicology, Research Triangle Park, NC, 27709
Ann NY Acad Sci; 381:43-53 1982

2. PRODUCTION OF BRAIN TUMORS WITH AROMATIC HYDROCARBONS.
Zimmerman HM
Montefiore Hosp. and Medical Center, 111 East 210th St., Bronx, NY, 10467
Ann NY Acad Sci; 381:320-324 1982

3. ORAL CONTRACEPTIVE STEROIDS AND MALIGNANCY.
Grant E
No affiliation given
Clin Oncol; 8(2):97-102 1982

4. METAL CARCINOGENESIS - WHAT IS REAL (MEETING ABSTRACT).
Furst A
Institute of Chemical Biology, University of San Francisco, San Francisco, CA, 94117
Environmental Analytical Chemistry, Airborne Mutagens and Carcinogens, June 16-18, 1982, Provo, Utah. Electric Power Research Institute 44 pp., 1982.

5. GENETIC EFFECTS OF N-METHYL-N'-NITRO-N-NITROSOGUANIDINE AND ITS HOMOLOGS.
Gichner T, Veleminsky J
Inst. Experimental Botany, Czechoslovak Acad. Sciences, Flemingovo 2, 160 00 Praha 6, Czechoslovakia
Mutat Res; 99(2):129-242 1982

RADIATION CARCINOGENESIS

6. PROBLEMS IN ASSESSING THE CANCER RISKS OF LOW-LEVEL IONIZING RADIATION EXPOSURE. VOLUME 1.
Comptroller General of the United States
(c/o Superintendent of Documents), United States General Accounting Office, Document Handling and Information Services Facility, P.O. Box 6015, Gaithersburg, MD, 20760
Problems in Assessing the Cancer Risks of Low-Level Ionizing Radiation Exposure. Volume 1. Washington, D. C., U. S. General Accounting Office, 85 pp., 1981.

7. PROBLEMS IN ASSESSING THE CANCER RISKS OF LOW-LEVEL IONIZING RADIATION EXPOSURE. VOLUME 2.
Comptroller General of the United States
(c/o Superintendent of Documents), United States General Accounting Office, Document Handling and Information Services, P.O. Box 6015, Gaithersburg, MD, 20760
Problems in Assessing the Cancer Risks of Low-Level Ionizing Radiation Exposure. Volume 2. Washington, D. C., U. S. General Accounting Office, 690 pp., 1981.

8. RISKS OF NUCLEAR ENERGY AND LOW-LEVEL IONIZING RADIATION. REPORT OF AN AMA ADVISORY PANEL TO THE COUNCIL ON SCIENTIFIC AFFAIRS OF THE AMERICAN MEDICAL ASSOCIATION.
Ashare AB, Lave LB, Lincoln TA, Lushbaugh CC, Murray SS, Saenger EL, Schaefer WW, Tupper CJ, Wald N
Dept. Nuclear Medicine, St. Elizabeth's Hosp., Boston, MA
Risks of Nuclear Energy and Low-Level Ionizing Radiation. Report of an AMA Advisory Panel to the Council on Scientific Affairs of the American Medical Association. Monroe, WI, American Medical Association, 40 pp., 1981.

9. ESTIMATION OF RISK OF CANCER INDUCTION IN POPULATIONS EXPOSED TO LOW-LEVEL RADIATION.
Fabrikant JI
Donner Lab., Univ. California, Berkeley, CA, 94720
Invest Radiol; 17(4):342-349 1982

10. EVOLUTION OF THE CONCEPTS AND STANDARDS OF RADIATION PROTECTION.
Xie Z
Inst. Nuclear Energy Academia Sinica, People's Republic of China
Zhonghua Fangsheyixue Yu Fanghu Zazhi; 1(1):2-12 1981
In CHI

11. IONIZING RADIATIONS: DNA DAMAGE, MUTAGENICITY AND MORPHOLOGICAL TRANSFORMATION IN MAMMALIAN CELLS. CARCINOGENICITY IN RODENTS AND IN HUMAN.
Parodi S, Taningher M, Toma S, Scarpati D, Santi L
Dept. Oncology, Genoa Univ., Genoa, Italy
Acta Thermogr; 6(1-3):10-15 1981

DIETARY FACTORS IN CARCINOGENESIS

12. CONTROLLING CADMIUM IN THE HUMAN FOOD CHAIN: A REVIEW AND RATIONALE BASED ON HEALTH EFFECTS.
Ryan JA, Pahren HR, Lucas JB
Municipal Environmental Res. Lab., U.S. Environmental Protection Agency, Cincinnati, OH, 45268
Environ Res; 28(2):251-302 1982

EPIDEMIOLOGY, ETIOLOGY AND GENETIC ASPECTS OF HUMAN CANCER

13. THE EPIDEMIOLOGY OF CANCER IN CHINA.
Armstrong B
Dept. Medicine, Univ. Western Australia, Queen Elizabeth II Medical Centre, Nedlands, Western Australia, Australia
World Health Forum; 3(1):95-101 1982

14. EPIDEMIOLOGY OF CANCER OF THE ENDOMETRIUM.
Mahboubi E, Eyler N, Wynder EL
Mahoney Inst. for Health Maintenance, American Health Foundation, New York, NY
Clin Obstet Gynecol; 25(1):5-17 1982

15. HOW TO PREVENT CANCER OF STOMACH AND COLON: SMALL MICROBES ARE BIG PRODUCERS OF CARCINOGENS.
Stortebecker P
Akerbyvagen 282, S-183 35 Taby/Stockholm, Sweden
How to Prevent Cancer of Stomach and Colon: Small Microbes are Big Producers of Carcinogens. Stockholm, Stortebecker Foundation for Research, 72 pp., 1981.

16. RELEVANCE OF COLONIC MUCOSAL INFLAMMATION TO AETIOLOGY.
Earnshaw P, Busuttil A, Ferguson A
Gastrointestinal Unit, Univ. Edinburgh, Edinburgh EH4 2XU, England
Recent Results Cancer Res; 83:31-44 1982

17. COLORECTAL CANCER: ETIOLOGY.
Kinlen LJ
Cancer Res. Campaign, Radcliffe Infirmary, Oxford OX2 6HE, England
Recent Results Cancer Res; 83:11-20 1982

18. ACUTE MYELOID LEUKEMIA FOLLOWING TREATMENT OF HODGKIN'S DISEASE. A REVIEW.
Grunwald HW, Rosner F
(c/o Rosner), Queen Hosp. Center Affiliation, Long Island Jewish-Hillside Medical Center, 82-68 164th St., Jamaica, NY, 11432
Cancer; 50(4):676-683 1982

19. PEUTZ-JEGHERS SYNDROME AND BILATERAL BREAST CARCINOMA.
Trau H, Schewach-Millet M, Fisher BK, Tsur H
Dept. Dermatology, Chaim Sheba Medical Center, Tel-Hashomer, Israel
Cancer; 50(4):788-792 1982

ENVIRONMENTAL AND OCCUPATIONAL FACTORS IN CARCINOGENESIS

20. HEALTH EFFECTS OF EXPOSURE TO DIESEL EXHAUST: IMPACTS OF DIESEL-POWERED LIGHT-DUTY VEHICLES.
Griffin HE, Brusick DJ, Castagnoli N, Crump KS, Goldschmidt BM, Higgins IT, Hoffmann D, Horvath SM, Nettesheim P, Stuart BO, Witschi H
Graduate Sch. Public Health San Diego State Univ., San Diego, CA
Health Effects of Exposure to Diesel Exhaust: Impacts of Diesel-Powered Light-Duty Vehicles. Washington, D. C., National Academy Press, , 169 pp., 1981.)

21. IARC MONOGRAPHS ON THE EVALUATION OF THE CARCINOGENIC RISK OF CHEMICALS TO HUMANS: THE RUBBER INDUSTRY.
IARC Working Group
Div. Environmental Carcinogenesis, International Agency for Res. on Cancer, Lyon, France
IARC Monogr Eval Carcinog Risk Chem Hum 28: 486 pp., 1982.

CELLULAR AND MOLECULAR MECHANISMS IN CARCINOGENESIS

22. CONCEPTS IN DRUG METABOLISM. PART B.
Jenner P, Testa B
Univ. Dept. Neurology, Inst. Psychiatry, London, England
Concepts in Drug Metabolism. Part B. New York, Marcel Dekker, Inc., Drugs and Pharmaceutical Science, Vol. 10, 627 pp., 1981.

23. CARCINOGENESIS, VASCULAR DISEASE, AND THE FREE RADICAL REACTION.
Johnson FC
Hall House Cottage, The St., Rickinghall, Diss, Norfolk IP22 1EG, England
Nutr Cancer; 3(3):117-121 1982

24. DNA MODIFICATION AND REPAIR IN THE EXPERIMENTAL INDUCTION OF NERVOUS SYSTEM TUMORS BY CHEMICAL CARCINOGENS.
Kleihues P, Patzschke K, Doerjer G
Pathologisches Institut, Albert Str. 19, 78 Freiburg, W. Germany
Ann NY Acad Sci; 381:290-303 1982

25. DNA REPAIR: A LABORATORY MANUAL OF RESEARCH PROCEDURES. VOLUME 1-PART A.
Friedberg EC, Hanawalt PC
Dept. Pathology, Stanford Univ., Stanford, CA
DNA Repair: A Laboratory Manual of Research Procedures. Volume 1 - Part A. New York, Marcel Dekker Inc., 273 pp., 1981.

26. DNA REPAIR: A LABORATORY MANUAL OF RESEARCH PROCEDURES. VOLUME 1-PART B.
Friedberg EC, Hanawalt PC
Dept. Pathology, Stanford Univ., Stanford, CA
DNA Repair: A Laboratory Manual of Research Procedures. Volume 1 - Part B. New York, Marcel Dekker Inc., 360 pp., 1981.

MODIFICATION OF CARCINOGENESIS

27. RETINOIDS AS CHEMOPREVENTIVE AND ANTICANCER AGENTS IN INTACT ANIMALS (REVIEW).
Hill DL, Grubbs CJ
Southern Res. Inst., Box 3307-A, Birmingham, AL, 35255
Anticancer Res; 2(1/2):111-124 1982

VIRAL AND IMMUNOLOGICAL ASPECTS OF CARCINOGENESIS

28. THE CONTRIBUTION OF THE VIRAL THEORY OF TUMOR ORIGIN TO ONCOLOGY.
Mazurenko NP
Center Oncology Res., USSR Acad. Medical Sciences, Moscow, USSR
Vopr Onkol; 28(5):7-12 1982
In RUS

29. PERSPECTIVES ON ENDOGENOUS RETROVIRUSES IN NORMAL AND PATHOLOGICAL GROWTH.
Weiss RA
Inst. Cancer Res., Fulham Road, London SW3 6JB, England
Curr Top Microbiol Immunol; 98:127-132 1982

30. ENDOGENOUS RETROVIRUSES OF MICE AND CHICKENS.
Steffen DL, Robinson H
Worcester Foundation Experimental Biology, 222 Maple Ave., Shrewsbury, MA, 01545
Curr Top Microbiol Immunol; 98:1-10 1982

31. POSSIBLE IMMUNOLOGICAL MECHANISMS IN C-TYPE VIRAL LEUKEMOGENESIS IN MICE.
Ihle JN, Lee JC
Biological Carcinogenesis Program, Frederick Cancer Res. Center, Frederick, MD
Curr Top Microbiol Immunol; 98:85-101 1982

32. ONCOVIRAL PROTEINS AS CELLULAR ANTIGENS.
Fleissner E, Snyder HW
Memorial Sloan-Kettering Cancer Inst., 1275 York Ave., New York, NY, 10021
Curr Top Microbiol Immunol; 98:37-80 1982

33. GENITAL WARTS: RECENT ADVANCES.
Oriel JD
Dept. Genito-Urinary Medicine, Univ. Coll Hosp., London, England
Clin Exp Dermatol; 7(4):361-367 1982

34. PRIMARY HEPATOCELLULAR CARCINOMA AND HEPATITIS B VIRUS.
Blumberg BS, London WT
Dept. Medicine, Univ. Pennsylvania, Philadelphia, PA
Curr Probl Cancer; 6(12):1-23 1982

35. IMMUNOLOGICAL ASPECTS OF EXPERIMENTAL BRAIN TUMORS. (REVIEW).
Stavrou D, Bilzer T, Hulten M, Zanker KS, Anzil AP, Haglid KG, Dahme E
Dept. Functional Pathology, Univ. Munich, 8 Koniginstr., 8000 Munich 22, W. Germany
Anticancer Res; 2(3):151-155 1982

METHODOLOGY IN CARCINOGENESIS RESEARCH

36. MUTAGEN ASSAY WITH ARABIDOPSIS: A REPORT OF THE U. S. ENVIRONMENTAL PROTECTION AGENCY GENE-TOX PROGRAM.
Redei GP
Univ. Missouri, Columbia, MO, 65211
Mutat Res; 99(2):243-255 1982

37. METABOLIC AND MODULATING FACTORS IN TOXICITY AND CHEMICAL CARCINOGENESIS (MEETING ABSTRACT).
Fishbein L

National Center for Toxicological Research, Jefferson, AR

1st World Congress on Toxicology and Environmental Health, May 27-30, 1982, Washington, D.C. American College of Toxicology 28 pp., 1982.

38. PROCEEDINGS OF THE INHALATION TOXICOLOGY AND TECHNOLOGY SYMPOSIUM HELD IN KALAMAZOO, MI, 23-24 OCTOBER, 1980.

Leong BK

Industrial Toxicology Lab., Upjohn Co., Kalamazoo, MI, 49001

Proceedings of the Inhalation Toxicology and Technology Symposium held in Kalamazoo, MI, 23-24 October, 1980. Ann Arbor, MI, Ann Arbor Science Publishers, Inc., 313 pp., 1981.

39. CHEMICAL CLASS SEPARATION AND DETAILED IDENTIFICATION OF GENOTOXIC POLYCYCLIC AROMATIC COMPOUNDS IN AIRBORNE PARTICULATES (MEETING ABSTRACT).

Later DW, Lee ML

Department of Chemistry, Brigham Young University, Provo, UT, 84602

Environmental Analytical Chemistry, Airborne Mutagens and Carcinogens, June 16-18, 1982, Provo, Utah. Electric Power Research Institute 44 pp., 1982.

OTHER REVIEWS IN CARCINOGENESIS

40. SPONTANEOUS NEOPLASTIC PATHOLOGY IN CONTROL RATS - A REVIEW.

Nunziata A, Storino AA

Centro Ricerca Farmaceutica, Via Tito Speri, 14 Pomezia, Roma, Italy

Vet Hum Toxicol; 24(4):243-247 1982

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